CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074852

Trade Name : DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE CAPSULE USP

Generic Name: Diltiazem Hydrochloride Extended-Release Capsule USP 120mg, 180mg and 240mg

Sponsor : Andrx Pharmaceuticals, Inc.

Approval Date: October 10, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074852

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074852

APPROVAL LETTER

ANDA 74-852

OCT 10 1997

Andrx Pharmaceuticals, Inc.
Attention: David A. Gardner
4001 S. W. 47th Avenue, Suite 201
Fort Lauderdale, FL 33314

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated December 19, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act) for Diltiazem Hydrochloride Extended-release Capsules USP, 120 mg, 180 mg and 240 mg.

Reference is also made to your amendments dated June 28 and September 5, 1996; and April 24, June 10, July 11, and August 5, 1997.

The listed drug product referenced in your application is subject to a period of patent protection which expires on December 9, 2006 (patent 4,839,177 [the '177 patent]), and June 6, 2012 (patent 5,422,123 [the '123 patent]). Your ANDA contains a paragraph IV certification to the '177 patent. The resulting lawsuit (Jagotec AG, Jago Research AG, Rhone Poulenc Rorer Pharmaceuticals Inc., and Rhone-Poulenc Rorer, Inc. v. Andrx Corporation, Inc. and Andrx Pharmaceuticals, Inc., Civil Action No. 96-1274-CIV-KEHOE), which did not include a determination of the merits of the patent infrigement claims, ended in the United States District Court for the Southern District of Florida with a final judgement of dismissal. In addition and in accordance with 21 CFR 314.94(a)(12)(vi), Andrx is not required to submit a patent certification for the '123 patent.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Diltiazem Hydrochloride Extended-release Capsules USP, 120 mg, 180 mg and 240 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Dilacor XR™ Capsules, 120 mg, 180 mg and 240 mg, respectively, of Rhone-Poulenc Rorer Pharmaceuticals Inc.).

Your "interim" dissolution testing should be incorporated into the stability and quality control program using the same method outlined in our March 21, 1997, correspondence. The "interim" dissolution test(s) and tolerances are:

> The dissolution testing should be conducted in 900 mL of acetate buffer pH 4.2 at 37% using USP 23 apparatus II (paddle) at 100 rpm. The test product should meet the following tentative specifications:

Time (hr)	Amount Dissolved
1	[redacted]#4 -
4	nfident
10	usines
15	

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches in a supplemental application. The supplemental application should be submitted under 21 CFR 314.70(c)(1) when there are no revisions to the interim specifications or when the final specifications are tighter than the interim specifications. In all other instances the supplement should be submitted under 21 CFR 314.70(b)(2)(ii).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074852

FINAL PRINTED LABELING

Andrx
PHARMACEUTICALS, INC.

NDC 62037-549-01

Diltiazem HCl

EXTENDED-RELEASE CAPSULES, USP

ONCE-A-DAY DOSAGE

180 mg

100 Capsules

Each Capsule Provides:
Diltiazem Hydrochloride ..... 180 mg

CAUTION: Federal law prohibits dispensing without prescription.

See insert for professional information.

Keep tightly closed.

Store at controlled room temperature, 15°-30°C (59°-86°F).

Dispense in tight, light resistant container as defined in USP.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

7021 (06/97)

N 3 62037-549-01 4

LOT:

EXP:

Andrx
PHARMACEUTICALS, INC.

NDC 62037-548-01

Diltiazem HCl

EXTENDED-RELEASE CAPSULES, USP

ONCE-A-DAY DOSAGE

120 mg

100 Capsules

Each Capsule Provides:
Diltiazem Hydrochloride ..... 120 mg

CAUTION: Federal law prohibits dispensing without prescription.

See insert for professional information.

Keep tightly closed.

Store at controlled room temperature, 15°-30°C (59°-86°F).

Dispense in tight, light resistant container as defined in USP.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

7018 (06/97)

N 3 62037-548-01 7

LOT:

EXP:

Andrx
PHARMACEUTICALS, INC.

NDC 62037-550-05

Diltiazem HCl

EXTENDED-RELEASE CAPSULES, USP

ONCE-A-DAY DOSAGE

240 mg

Each Capsule Provides:
Diltiazem Hydrochloride ..... 240 mg

CAUTION: Federal law prohibits dispensing without prescription.

See insert for professional information.

Keep tightly closed.

Store at controlled room temperature, 15°-30°C (59°-86°F).

Dispense in tight, light resistant container as defined in USP.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

7025 (06/97)

N 3 62037-550-05 8

LOT:

EXP:

Andrx
PHARMACEUTICALS, INC.

NDC 62037-550-01

Diltiazem HCl

EXTENDED-RELEASE
CAPSULES, USP

ONCE-A-DAY DOSAGE

240 mg

100 Capsules

Each Capsule Provides:
Diltiazem Hydrochloride ..... 240 mg

CAUTION: Federal law prohibits dispensing without prescription.

See insert for professional information.

Keep tightly closed.

Store at controlled room temperature, 15°-30°C (59°-86°F).

Dispense in tight, light resistant container as defined in USP.

7024 (06/97)

N 3 62037-550-01 0

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

LOT:

EXP.:

Andrx
PHARMACEUTICALS, INC.

NDC 62037-548-10

Diltiazem HCl

EXTENDED-RELEASE CAPSULES, USP

ONCE-A-DAY DOSAGE

120 mg

1000 Capsules

7020 (06/97)

Each Capsule Provides:
Diltiazem Hydrochloride ..... 120 mg

CAUTION: Federal law prohibits dispensing without prescription.

See insert for professional information.

Keep tightly closed.

Store at controlled room temperature, 15°-30°C (59°-86°F).

Dispense in tight, light resistant container as defined in USP.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

N 3 62037-548-10 9

LOT:

EXP.:

Andrx
PHARMACEUTICALS, INC.

NDC 62037-550-10

Diltiazem HCl

EXTENDED-RELEASE CAPSULES, USP

ONCE-A-DAY DOSAGE

240 mg

7026 (06/97)

Each Capsule Provides:
Diltiazem Hydrochloride ..... 240 mg

CAUTION: Federal law prohibits dispensing without prescription.

See insert for professional information.

Keep tightly closed.

Store at controlled room temperature, 15°-30°C (59°-86°F).

Dispense in tight, light resistant container as defined in USP.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

N 3 62037-550-10 2

LOT:

EXP.:

Andrx
PHARMACEUTICALS, INC.

NDC 62037-548-05

Diltiazem HCl

EXTENDED-RELEASE CAPSULES, USP

ONCE-A-DAY DOSAGE

120 mg

500 Capsules

7019 (06/97)

Each Capsule Provides:
Diltiazem Hydrochloride ..... 120 mg

CAUTION: Federal law prohibits dispensing without prescription.

See insert for professional information.

Keep tightly closed.

Store at controlled room temperature, 15°-30°C (59°-86°F).

Dispense in tight, light resistant container as defined in USP.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

N 3 62037-548-05 5

LOT:

EXP.:

Andrx
PHARMACEUTICALS, INC.

NDC 62037-549-05

Diltiazem HCl

EXTENDED-RELEASE CAPSULES, USP

ONCE-A-DAY DOSAGE

180 mg

500 Capsules

7022 (06/97)

Each Capsule Provides:
Diltiazem Hydrochloride ..... 180 mg

CAUTION: Federal law prohibits dispensing without prescription.

See insert for professional information.

Keep tightly closed.

Store at controlled room temperature, 15°-30°C (59°-86°F).

Dispense in tight, light resistant container as defined in USP.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

N 3 62037-549-05 2

LOT:

EXP.:

Andrx
PHARMACEUTICALS, INC.

NDC 62037-549-10

Diltiazem HCl

EXTENDED-RELEASE CAPSULES, USP

ONCE-A-DAY DOSAGE

180 mg

1000 Capsules

7023 (06/97)

Each Capsule Provides:
Diltiazem Hydrochloride ..... 180 mg

CAUTION: Federal law prohibits dispensing without prescription.

See insert for professional information.

Keep tightly closed.

Store at controlled room temperature, 15° 30°C (59°-86°F).

Dispense in tight, light resistant container as defined in USP.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

N 3 62037-549-10 6

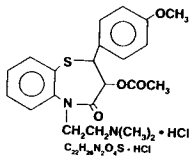
LOT:

EXP.:

Diltiazem Hydrochloride Extended-release Capsules, USP
(Once-a-day dosage)

DESCRIPTION

Diltiazem hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-benzothiazepin-4(5H)-one, 3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+)-cis-. Its molecular formula is $C_{22}H_{26}N_2O_4S \cdot HCl$ and its molecular weight is 450.99. Its structural formula is as follows:



$C_{22}H_{26}N_2O_4S \cdot HCl$

Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform.

Each diltiazem hydrochloride extended-release capsule (once daily dosage), for oral administration, contains multiple units of diltiazem HCl Extended-release, 60 mg, resulting in 120 mg, 180 mg or 240 mg dosage strengths allowing for the controlled release of diltiazem hydrochloride over a 24-hour period.

Inactive Ingredients: Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) also contain acetyltributyl citrate, lactose (anhydrous), hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, magnesium stearate, colloidal silicon dioxide, dibasic sodium phosphate, talc, gelatin, black iron oxide, D & C Yellow # 10 aluminum lake, FD & C blue # 1 aluminum lake, FD & C blue # 2 aluminum lake, FD & C red # 40 aluminum lake, and titanium dioxide. The 180 mg and 240 mg dosage forms also contain yellow iron oxide.

USP drug release test pending.

CLINICAL PHARMACOLOGY

The therapeutic benefits of diltiazem hydrochloride are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Hypertension. Diltiazem produces the antihypertensive effect primarily by relaxation of vascular smooth muscle with a resultant decrease in peripheral vascular resistance. The magnitude of blood pressure reduction is related to the degree of hypertension; thus hypertensive individuals experience an antihypertensive effect, whereas there is only a modest fall in blood pressure in normotensives.

Angina. Diltiazem HCl has been shown to produce increases in exercise tolerance probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal work loads.

Diltiazem has been shown to be a potent dilator of coronary arteries, both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by diltiazem.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atri-

the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure in normotensive individuals. In exercise tolerance studies in patients with ischemic heart disease, diltiazem reduces the double product (HR x SBP) for any given workload. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect. Cardiac output, ejection fraction and left ventricular end diastolic pressure have not been affected. Such data have no predictive value with respect to effects in patients with poor ventricular function. Increased heart failure has, however, been reported in occasional patients with preexisting impairment of ventricular function. There are as yet few data on the interaction of diltiazem and beta-blockers in patients with poor ventricular function. Resting heart rate is usually slightly reduced by diltiazem.

Diltiazem Hydrochloride Extended-release Capsules produce antihypertensive effects both in the supine and standing positions. Postural hypotension is infrequently noted upon suddenly assuming an upright position. Diltiazem decreases vascular resistance, increases cardiac output (by increasing stroke volume), and produces a slight decrease or no change in heart rate. No reflex tachycardia is associated with the chronic antihypertensive effects.

During dynamic exercise, increases in diastolic pressure are inhibited while maximum achievable systolic pressure is usually reduced. Heart rate at maximum exercise does not change or is slightly reduced.

Diltiazem antagonizes the renal and peripheral effects of angiotensin II. No increased activity of the renin-angiotensin-aldosterone axis has been observed. Chronic therapy with diltiazem produces no change or an increase in plasma catecholamines. Hypertensive animal models respond to diltiazem with reductions in blood pressure and increased urinary output and natriuresis without a change in the urinary sodium/potassium ratio. In man, transient natriuresis and kaliuresis have been reported, but only in high intravenous doses of 0.5 mg/kg of body weight.

Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases). Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%.

In two short-term, double-blind, placebo-controlled studies, 303 hypertensive patients were treated with once-daily diltiazem hydrochloride extended-release capsules in doses of up to 540 mg. There were no instances of greater than first-degree atrioventricular block, and the maximum increase in the PR interval was .08 seconds. No patients were prematurely discontinued from the medication due to symptoms related to prolongation of the PR interval.

Pharmacodynamics. In one short-term, double-blind, placebo-controlled study, diltiazem hydrochloride extended-release capsule in doses of 120, 240, 360, and 480 mg/day demonstrated a dose-related antihypertensive response among patients with mild to moderate hypertension. Statistically significant decreases in trough mean supine diastolic blood pressure were seen through four weeks of treatment: 120 mg/day (-5.1 mmHg); 240 mg/day (-6.9 mmHg); 360 mg/day (-6.9 mmHg); and, 480 mg/day (-10.6 mmHg). Statistically significant decreases in trough mean supine systolic blood pressure were also seen through four weeks of treatment: 120 mg/day (-2.6 mmHg); 240 mg/day (-6.5 mmHg); 360 mg/day (-4.8 mmHg); and, 480 mg/day (-10.6 mmHg). The proportion of evaluable patients exhibiting a therapeutic response (supine diastolic blood pressure <90 mmHg or decrease >10 mmHg) was greater as the dose increased: 31%, 42%, 48% and 69% with the 120, 240, 360 and 480 mg/day diltiazem groups, respectively. Similar findings were observed for standing systolic and diastolic blood pressures. The trough (24 hours after a dose) antihypertensive effect of diltiazem hydrochloride extended-release capsule retained more than one-half of the response seen at peak (3-6 hours after administration).

Significant reductions of mean supine blood pressure (at trough) in patients with mild to moderate hypertension were also seen in a short-term, double-blind, dose-escalation, placebo-controlled study after 2 weeks of a once-daily diltiazem hydrochloride extended-release capsule 180 mg/day (diastolic: -6.1 mmHg, systolic: -4.7 mmHg) and again, 2 weeks after escalation to 360 mg/day (diastolic: -9.3 mmHg; systolic: -7.2 mmHg). However, a further increase in dose to 540 mg/day for 2 weeks provided only a minimal further increase in the antihypertensive effect (diastolic: -10.2 mmHg; systolic: -6.7 mmHg).

Diltiazem hydrochloride extended-release capsule given at 120 mg, 240 mg, and 480 mg/day, in a randomized, multicenter, double-blind, placebo-controlled, parallel group, dose-ranging study, in 189 patients with chronic angi-

the 120, 240, 360 and 480 mg/day diltiazem groups, respectively. Similar findings were observed for standing systolic and diastolic blood pressures. The trough (24 hours after a dose) antihypertensive effect of diltiazem hydrochloride extended-release capsule retained more than one-half of the response seen at peak (3-6 hours after administration).

Significant reductions of mean supine blood pressure (at trough) in patients with mild to moderate hypertension were also seen in a short-term, double-blind, dose-escalation, placebo-controlled study after 2 weeks of a once-daily diltiazem hydrochloride extended-release capsule 180 mg/day (diastolic: -6.1 mmHg; systolic: -4.7 mmHg) and again, 2 weeks after escalation to 360 mg/day (diastolic: -9.3 mmHg; systolic: -7.2 mmHg). However, a further increase in dose to 540 mg/day for 2 weeks provided only a minimal further increase in the antihypertensive effect (diastolic: -10.2 mmHg; systolic: -6.7 mmHg).

Diltiazem hydrochloride extended-release capsule given at 120 mg, 240 mg, and 480 mg/day, in a randomized, multicenter, double-blind, placebo-controlled, parallel group, dose-ranging study, in 189 patients with chronic angina, demonstrated a dose-related increase in exercise time by Exercise Tolerance Test (ETT) and a reduction in rates of anginal attacks (based on individual patients diaries). The improvement in total exercise time (using the Bruce protocol), measured at trough exercise periods, for placebo, 120 mg, 240 mg, and 480 mg, was 20, 37, 49, and 56 seconds, respectively.

Pharmacokinetics and Metabolism.

Diltiazem is well absorbed from the gastrointestinal tract, and is subject to an extensive first-pass effect. When given as an immediate release oral formulation, the absolute bioavailability (compared to intravenous administration) of diltiazem is approximately 40%. Diltiazem undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. Total radioactivity measurement following short IV administration in healthy volunteers suggests the presence of other unidentified metabolites which attain higher concentrations than those of diltiazem and are more slowly eliminated; half-life of total radioactivity is about 20 hours compared to 2 to 5 hours for diltiazem. *In-vitro* binding studies show diltiazem HCl is 70% to 80% bound to plasma proteins. Competitive *in-vitro* ligand binding studies have also shown diltiazem HCl binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. The plasma elimination half-life of diltiazem is approximately 3.0 to 4.5 hours. Desacetyldiltiazem, the major metabolite of diltiazem, which is also present in the plasma at concentrations of 10% to 20% of the parent drug, is approximately 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of diltiazem hydrochloride appear to be in the range of 40-200 ng/mL. There is a departure from linearity when dose strengths are increased; the half-life is slightly increased with dose.

A study that compared patients with normal hepatic function to patients with cirrhosis found an increase in half-life and a 69% increase in bioavailability in the hepatically impaired patients. Patients with severely impaired renal function showed no difference in the pharmacokinetic profile of diltiazem compared to patients with normal renal function.

Diltiazem Hydrochloride Extended-release Capsules contain a degradable controlled-release tablet formulation designed to release diltiazem over a 24-hour period. Controlled absorption of diltiazem begins within 1 hour, with maximum plasma concentrations being achieved 4 to 6 hours after administration. The apparent steady-state half-life of diltiazem following once-daily administration of Diltiazem Hydrochloride Extended-release Capsules ranges from 5 to 10 hours. This prolongation of half-life is attributed to continued absorption of diltiazem rather than alteration in its elimination.

The absolute bioavailability of diltiazem from a single dose of diltiazem hydrochloride extended release capsule (compared to intravenous administration) is 41% (±14). This value was shown to be similar to the 40% systemic availability reported following administration of an immediate release diltiazem hydrochloride formulation.

As the dose of a diltiazem hydrochloride extended-release capsule is increased from a daily dose of 120 mg to 240 mg, there is an increase in the AUC of 2.3 fold. When the dose is increased from 240 mg to 360 mg, AUC increases 1.6 fold and when increased from 240 mg to 480 mg, AUC increases 2.4 fold.

It has been reported *in-vivo* release of diltiazem occurs throughout the gastrointestinal tract, with controlled release still occurring for up to 24 hours after administration, as determined by radiolabeled methods. As the once-daily dose of Diltiazem Hydrochloride Extended-release Capsules was increased, departures from linearity were noted. There were disproportionate increases in area under the curve for doses from 120 mg to 480 mg.

The presence of food did not affect the ability of Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) to maintain a controlled release of the drug and did not impact its sustained release properties over 24-hours after administration. However, simultaneous administration of Diltiazem Hydrochloride Extended-release Capsules (Once-a-day Dosage) with a high-fat breakfast resulted in increases in AUC of 13% and 19%, and in C_{max} by 37% and 51% respectively.

INDICATIONS AND USAGE

Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) are indicated for the treatment of hypertension. Diltiazem hydrochloride may be used alone or in combination with other antihypertensive medications, such as diuretics.

extended-release capsule is increased from a daily dose of 120 mg to 240 mg, there is an increase in the AUC of 2.3 fold. When the dose is increased from 240 mg to 360 mg, AUC increases 1.6 fold and when increased from 240 mg to 480 mg, AUC increases 2.4 fold.

It has been reported in vivo release of diltiazem occurs throughout the gastrointestinal tract, with controlled release still occurring for up to 24 hours after administration, as determined by radiolabeled methods. As the once-daily dose of Diltiazem Hydrochloride Extended-release Capsules was increased, departures from linearity were noted. There were disproportionate increases in area under the curve for doses from 120 mg to 480 mg.

The presence of food did not affect the ability of Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) to maintain a controlled release of the drug and did not impact its sustained release properties over 24-hours after administration. However, simultaneous administration of Diltiazem Hydrochloride Extended-release Capsules (Once-a-day Dosage) with a high-fat breakfast resulted in increases in AUC of 13% and 19%, and in C_{max} by 37% and 51% respectively.

INDICATIONS AND USAGE

Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) are indicated for the treatment of hypertension. Diltiazem hydrochloride may be used alone or in combination with other antihypertensive medications, such as diuretics.

Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage) are indicated for the management of chronic stable angina.

CONTRAINDICATIONS

Diltiazem hydrochloride is contraindicated in: **(1)** patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker; (2) patients with second or third degree AV block except in the presence of a functioning ventricular pacemaker; (3) patients with hypotension (less than 90 mmHg systolic); **(4)** patients who have demonstrated hypersensitivity to the drug; and (5) patients with acute myocardial infarction and pulmonary congestion as documented by X-ray on admission.

WARNINGS

1. Cardiac Conduction. Diltiazem hydrochloride prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second, or third degree AV block (22 of 10,119 patients, or 0.2%); **41%** of these 22 patients were receiving concomitant β-adrenoceptor antagonists versus 17% of the total group. Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single 60 mg dose of diltiazem.

2. Congestive Heart Failure. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction of 24% ±6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of diltiazem hydrochloride in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. Hypotension. Decreases in blood pressure associated with diltiazem hydrochloride therapy may occasionally result in symptomatic hypotension.

4. Acute Hepatic Injury. Mild elevations of serum transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 6 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to diltiazem is uncertain in some cases, but probable in some others (see PRECAUTIONS).

PRECAUTIONS

General. Diltiazem hydrochloride is extensively metabolized by the liver and is excreted by the kidneys and in bile. As with any drug given over prolonged peri-

ods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing. Dermatological events (see ADVERSE REACTIONS) may be transient and may disappear despite continued use of diltiazem hydrochloride. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Although Diltiazem Hydrochloride Extended-release Capsules utilize a slowly disintegrating matrix, caution should still be used in patients with pre-existing severe gastrointentinal narrowing (pathologic or iatrogenic). There have been no reports of obstructive symptoms in patients with known strictures in association with the ingestion of Diltiazem Hydrochloride Extended-release Capsules.

Information for Patients. Diltiazem Hydrochloride Extended-release Capsules should be taken on an empty stomach. Patients should be cautioned that the Diltiazem Hydrochloride Extended-release Capsules should not be opened, chewed or crushed, and should be swallowed whole.

Drug Interactions. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving diltiazem hydrochloride concomitantly with any agents known to affect cardiac contractility and/or conduction (see WARNINGS). Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with diltiazem hydrochloride (see WARNINGS). As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem hydrochloride undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of diltiazem hydrochloride with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Especially in patients with renal and/or hepatic impairment, dosages of similarly metabolized drugs, particularly those of low therapeutic ratio such as cyclosporin, may require adjustment when starting or stopping concomitantly administered diltiazem hydrochloride to maintain optimum therapeutic blood levels. Concomitant administration of diltiazem with carbamazepine has been reported to result in elevated plasma levels of carbamazepine, resulting in toxicity in some cases.

Beta-Blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of diltiazem hydrochloride and beta-blockers is usually well-tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of diltiazem hydrochloride concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted (see WARNINGS).

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of diltiazem hydrochloride with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing diltiazem hydrochloride therapy to avoid possible over- or under-digitalization (see WARNINGS).

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium channel blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and an 18-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response *in-vitro* or *in-vivo* in mammalian cell assays or *in-vitro* in bacteria. No evidence of impaired fertility was observed in male or female rats at oral doses of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats and rabbits. Administration of doses ranging from 4 to 6 times (depending on

dine. An adjustment in the diltiazem dose may be warranted.

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Pregnancy. Category C. Reproduction studies have been conducted in mice, rats and rabbits. Administration of doses ranging from 4 to 6 times (depending on species) the upper limit of the optimum dosage range in clinical trials (480 mg q.d. or 8 mg/kg q.d. for a 60 kg patient) has resulted in embryo and fetal lethality. These studies have revealed, in one species or another, a propensity to cause abnormalities of the skeleton, heart, retina and tongue. Also observed were reductions in early individual pup weights and pup survival, prolonged delivery and increased incidence of stillbirths.

There are no well-controlled studies in pregnant women; therefore, use diltiazem hydrochloride in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of diltiazem hydrochloride is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Patients. Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Serious adverse reactions to diltiazem hydrochloride have been rare in studies with other formulations, as well as with Diltiazem Hydrochloride Extended-release Capsules. It should be recognized, however, that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

There have been post-marketing reports of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with the use of diltiazem hydrochloride.

Hypertension: The most common adverse events (frequency ≥1%) in placebo-controlled, clinical hypertension studies with diltiazem hydrochloride extended-release capsule using daily doses up to 540 mg, are listed in the table below with placebo-treated patients included for comparison.

MOST COMMON ADVERSE EVENTS IN DOUBLE-BLIND, PLACEBO-CONTROLLED HYPERTENSION TRIALS

	Diltiazem HCl Extended-release Capsules* (Once-a-day dosage)	Placebo
Adverse Events (COSTART Term)	**n=303 # pts (%)**	**n=87 # pts (%)**
rhinitis	29 (9.6)	7 (8.0)
headache	27 (8.9)	12 (13.8)
pharyngitis	17 (5.6)	4 (4.6)
constipation	11 (3.6)	2 (2.3)
cough increase	9 (3.0)	2 (2.3)
flu syndrome	7 (2.3)	1 (1.1)
edema, peripheral	7 (2.3)	0 (0.0)
myalgia	7 (2.3)	0 (0.0)
diarrhea	6 (2.0)	0 (0.0)
vomiting	6 (2.0)	0 (0.0)
sinusitis	6 (2.0)	1 (1.1)
asthenia	5 (1.7)	0 (0.0)
pain, back	5 (1.7)	2 (2.3)
nausea	5 (1.7)	1 (1.1)
dyspepsia	4 (1.3)	0 (0.0)
vasodilatation	4 (1.3)	0 (0.0)
injury, accident	4 (1.3)	0 (0.0)
pain, abdominal	3 (1.0)	0 (0.0)
arthrosis	3 (1.0)	0 (0.0)
insomnia	3 (1.0)	0 (0.0)
dyspnea	3 (1.0)	0 (0.0)
rash	3 (1.0)	1 (1.1)
tinnitus	3 (1.0)	0 (0.0)

*Adverse events occurring in 1% or more of patients receiving diltiazem hydrochloride extended-release capsule (once daily dosing).

Angina: The most common adverse events (frequency ≥ 1%) in a placebo-controlled, short-term (2 week) clinical angina study with diltiazem hydrochloride extended-release capsule (once daily dosing) are listed in the table below with placebo-treated patients included for comparison. In this trial, following a placebo phase, patients were randomly assigned to once-daily dose of either 120, 240 or 480 mg of diltiazem hydrochloride extended-release capsule (once daily dosing).

MOST COMMON ADVERSE EVENTS IN A DOUBLE-BLIND, PLACEBO-CONTROLLED SHORT-TERM, ANGINA TRIAL

	Diltiazem HCl Extended-release Capsules* (Once-a-day dosage)	Placebo
Adverse Events (COSTART Term)	**n=138 # pts (%)**	**n=50 # pts (%)**
asthenia	5 (3.6)	2 (4.0)
headache	4 (2.9)	3 (6.0)
pain, back	4 (2.9)	1 (2.0)
rhinitis	4 (2.9)	1 (2.0)
constipation	3 (2.2)	1 (2.0)
nausea	3 (2.2)	0 (0.0)
edema, peripheral	3 (2.2)	1 (2.0)
dizziness	3 (2.2)	0 (0.0)
cough, increased	3 (2.2)	0 (0.0)
bradycardia	2 (1.4)	0 (0.0)
fibrillation, atrial	2 (1.4)	0 (0.0)
arthralgia	2 (1.4)	0 (0.0)
dream, abnormal	2 (1.4)	0 (0.0)
dyspnea	2 (1.4)	0 (0.0)
pharyngitis	2 (1.4)	1 (2.0)

controlled, short-term (2 week) clinical angina study with diltiazem hydrochloride extended-release capsule (once daily dosing) are listed in the table below with placebo-treated patients included for comparison. In this trial, following a placebo phase, patients were randomly assigned to once-daily dose of either 120, 240 or 480 mg of diltiazem hydrochloride extended-release capsule (once daily dosing).

MOST COMMON ADVERSE EVENTS IN A DOUBLE-BLIND, PLACEBO-CONTROLLED SHORT-TERM, ANGINA TRIAL

	Diltiazem HCl Extended-release Capsules* (Once-a-day dosage)	Placebo
Adverse Events (COSTART Term)	n=139 # pts (%)	n=50 # pts (%)
asthenia	5 (3.6)	2 (4.0)
headache	4 (2.9)	3 (6.0)
pain, back	4 (2.9)	1 (2.0)
rhinitis	4 (2.9)	1 (2.0)
constipation	3 (2.2)	1 (2.0)
nausea	3 (2.2)	0 (0.0)
edema, peripheral	3 (2.2)	1 (2.0)
dizziness	3 (2.2)	0 (0.0)
cough, increased	3 (2.2)	0 (0.0)
bradycardia	2 (1.4)	0 (0.0)
fibrillation, atrial	2 (1.4)	0 (0.0)
arthralgia	2 (1.4)	0 (0.0)
dream, abnormal	2 (1.4)	0 (0.0)
dyspnea	2 (1.4)	0 (0.0)
pharyngitis	2 (1.4)	1 (2.0)

*Adverse events occurring in 1% or more of patients receiving diltiazem hydrochloride extended-release capsule (once daily dosing).

Infrequent Adverse Events. The following additional events (COSTART Terms), listed by body system, were reported infrequently (less than 1%) in all subjects, hypertensive (n=425) or angina (n=318) patients who received diltiazem hydrochloride extended-release capsules, or with other formulations of diltiazem.

Hypertension. Cardiovascular: First-degree AV block, arrhythmia, postural hypotension, tachycardia, pallor, palpitations, phlebitis, ECG abnormality, ST elevation.

Nervous System: Vertigo, hypertonia, paresthesia, dizziness, somnolence.

Digestive System: Dry mouth, anorexia, tooth disorder, eructation.

Skin and Appendages: Sweating, urticaria, skin hypertrophy (nevus).

Respiratory System: Epistaxis, bronchitis, respiratory disorder.

Urogenital System: Cystitis, kidney calculus, impotence, dysmenorrhea, vaginitis, prostate disease.

Metabolic and Nutritional Disorders: Gout, edema.

Musculoskeletal System: Arthralgia, bursitis, bone pain.

Hemic and Lymphatic System: Lymphadenopathy.

Body as a Whole: Pain, unevaluable reaction, neck pain, neck rigidity, fever, chest pain, malaise.

Special Senses: Amblyopia (blurred vision), ear pain.

Angina. Cardiovascular: Palpitations, AV block, sinus bradycardia, bigeminal extrasystole, angina pectoris, hypertension, hypotension, myocardial infarct, myocardial ischemia, syncope, vasodilatation, ventricular extrasystole.

Nervous System: Abnormal thinking, neuropathy, paresthesia.

Digestive System: Diarrhea, dyspepsia, vomiting, colitis, flatulence, GI hemorrhage, stomach ulcers.

Skin and Appendages: Contact dermatitis, pruritus, sweating.

Respiratory System: Respiratory distress.

Urogenital System: Kidney failure, pyelonephritis, urinary tract infection.

Metabolic and Nutritional Disorders: Weight increase.

Musculoskeletal System: Myalgia.

Body as a Whole: Chest pain, accidental injury, infection.

Special Senses: Eye hemorrhage, ophthalmitis, otitis media, taste perversion, tinnitus.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem hydrochloride has been limited. The administration of ipecac to induce vomiting and activated charcoal to reduce drug absorption have been advocated as initial means of intervention. In addition to gastric lavage, the following measures should also be considered.

Bradycardia: Administer atropine (0.60 mg to 1 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

High-Degree AV Block: Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.

Cardiac Failure: Administer inotropic agents (dopamine, or dobutamine) and diuretics.

Hypotension: Vasopressors (e.g. dopamine or norepinephrine).

Actual treatment and dosage should depend on the severity of the clinical situation as well as the judgment and experience of the treating physician.

Due to extensive metabolism, plasma concentrations after a standard dose of diltiazem can vary over tenfold, which significantly limits their value in evaluating cases of overdosage. Charcoal hemoperfusion has been used successfully as an adjunct therapy to hasten drug elimination. Overdoses with as much as 10.8 gm of oral diltiazem have been successfully treated using appropriate supportive care.

DOSAGE AND ADMINISTRATION

Hypertensive or anginal patients who are treated with other formulations of diltiazem can safely be switched to Diltiazem Hydrochloride Extended-release Capsules (Once-a-day dosage) at the nearest equivalent total daily dose. Subsequent titration to higher or lower doses may, however, be necessary and should be initiated as clinically indicated.

Studies have shown a slight increase in the rate of absorption of Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-day dosage), when ingested with a high-fat breakfast; therefore, administration in the morning on an empty stomach is recommended.

Patients should be cautioned that the Diltiazem Hydrochloride Extended-release

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074852

CHEMISTRY REVIEW(S)

D, N

1. CHEMIST'S REVIEW NO. 3

2. ANDA #74-852

3. NAME AND ADDRESS OF APPLICANT

Andrx Pharmaceuticals, Inc.
Attention: Mr. David A. Gardner
4001 S. W. 47th Avenue, Suite 201
Fort Lauderdale, FL 33314

4. LEGAL BASIS for ANDA SUBMISSION

Innovator Drug: Dilacor XR, Rhone-Plulenc Rorer.
NDA 20-092 Product Exclusivity - 5/29/95, 10/15/95
NCE Exclusivity - None indicated
The firm includes the following patent and expiration dating for this drug product.
U.S. 4,839,177 -12/9/2006
Andrx also includes reasons for which this patent will not be infringed on a case-by-case basis.
Note: Prior to the filing Andrx Pharmaceuticals had communicated with Center director Janet Woodcock, M.D., (in the form of citizen petition) for filing an ANDA that refers to the listed drug Dilacor XR (Rhone-Plulenc Rorer) rather than Cardizem CD, as the designated reference drug product. Dr. Woodcock had granted the petition.

5. SUPPLEMENT(s) None

6. PROPRIETARY NAME	7. NONPROPRIETARY NAME
Dilacor XR	Diltiazem Hydrochloride, Extended release capsules

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Firm:
12/19/1995- Original Application
4/10/1996 - ANDA Original minor amendment specification for in-process testing.
5/29/1996 - Information re: legal action by Rhone-Poulenc Rorer Pharma.
6/17/1996 - Minor amendment with revised stability data
7/1/1996 - Minor amendment for the Division of Bioequivalence
9/27/1996- Major amendment for Chemistry/labeling deficiencies
10/7/1996 - Minor amendment re: patent infringement information
4/24/97 - Minor amendment re: chemistry/labeling deficiencies
6/10/97- Minor amendment re: labeling deficiencies
7/11/97- Minor amendment re: labeling deficiencies
8/5/97- Minor amendment re: labeling deficiencies

FDA:
2/12/1996 - Date of receipt
8/13/1996 - Div. of Bioequivalence requested a minor amend.
8/27/1996 - Chemistry & labeling deficiency letter
3/21/97 -Chemistry minor deficiency letter
4/24/97 - Labeling minor deficiency letter
5/16/97- Review by Bio
5/29/97 - Chemistry review completed and satisfactory
7/11/97 -labeling minor deficiency letter
8/15/97- final satisfactory labeling review

10. PHARMACOLOGICAL CATEGORY — 11. Rx or OTC
Antihypertensive (antianginal) (Ca antagonist) — R_x

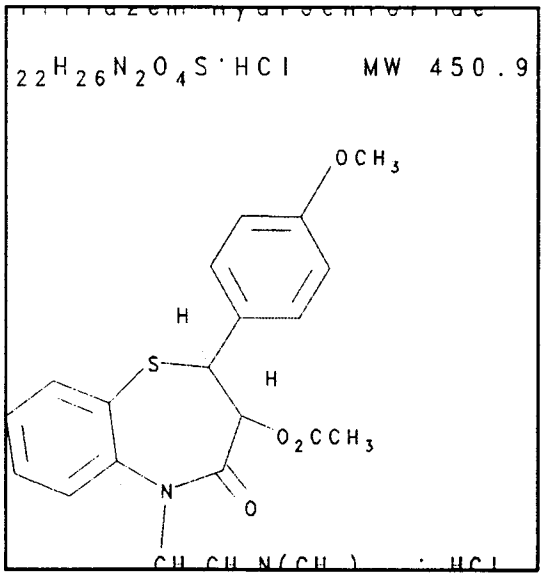
12. RELATED IND/NDA/DMF(s) See #37 for list of DMFs

13. DOSAGE FORM — 14. POTENCY

SR Capsules Oral — 120 mg, 180 mg, and 240 mg

15. CHEMICAL NAME AND STRUCTURE

(+)-5-[2-(Dimethylamino)ethyl]-*cis*-2,3-dihydro-3-hydroxy-2-(*p*-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one, acetate (ester) monohydrochloride [33286-22-5]



16. RECORDS AND REPORTS

None.

17. COMMENTS
    1. CMC review - Satisfactory
    2. EER is acceptable as of 7/23/97
    3. Method validation not required
    4. Bio review - by A. Jackson completed
    5. Labeling - by J. White completed and satisfactory on 8/15/97
    6. DMFs satisfactory for all referred

18. CONCLUSIONS AND RECOMMENDATIONS
    The application does not have any outstanding CMC deficiencies. Approved!

19. REVIEWER: DATE COMPLETED:

    Radhika Rajagopalan 8/15/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074852

BIOEQUIVALENCE REVIEW(S)

9 w

ANDA 74-852

AUG 13 1996

Andrx Pharmaceuticals, Inc
Attention: David A. Gardner
4001 SW 47th Avenue, Suite 201
Fort Lauderdale, FL 33314

Dear Mr. Gardner:

Reference is made to the Abbreviated New Drug Application, submitted on December 19, 1995, for Diltiazem Hydrochloride Extended- release Capsules, 120 mg, 180 mg and 240 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. Comparative dissolution testing was submitted for Diltiazem Hydrochloride Extended-Release Capsules, 120 mg, 180 mg and 240 mg, in water, SGF, pH 4.2, pH 6.2 and SIF.

2. In USP-supplement #3, page 2919, the following dissolution procedures are recommended: Test #2 in 900 mL water and Test #3 in 900 mL 0.1N HCl.

3. The test products did not meet USP specifications for Test #2 in water at any time point. Comparative dissolution in hydrochloric acid along with the dissolution method you plan to use along with the proposed dissolution specifications should be submitted in detail.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

AUG 5 1996

Diltiazem HCl XR Capsules
120 mg, 180 mg and 240 mg
ANDA #74-852
Reviewer: Moheb H. Makary
WP 74852SDW.D95

Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL
Submission Date:
December 19, 1955

Review of In Vivo Bioequivalence Studies, Dissolution Data and Waiver Requests

I. Objective:

The firm submitted three bioequivalence studies and dissolution data to assess the bioequivalence of the Andrx's Diltiazem HCl Extended-Release (XR) Capsules, 240 mg, to Rhone-Poulenc Rorer's Dilacor XR^R 240 mg Capsules. The firm requested a waiver of the in vivo bioequivalence testing requirements for its 120 mg and 180 mg strengths. To support the requests, the firm has submitted comparative dissolution profiles for its Diltiazem HCl Extended Release, 120 mg and 180 mg Capsules versus Dilacor XR^R 120 mg and 180 mg Capsules, respectively. The formulations for the drug products Diltiazem HCl Extended-Release 120 mg, 180 mg and 240 mg Capsules were also submitted.

The following studies were performed and included in the submission:

1. Study #P95-166
A two-way crossover, single-dose bioequivalence study of Diltiazem HCl extended-release (XR) 240 mg Capsules under fasting conditions.

2. Study #P95-165
A three-way crossover, single-dose, post-prandial bioequivalence study of Diltiazem HCl XR 240 mg Capsules.

3. Study #P95-167
A two-way crossover, multiple-dose bioequivalence study of Diltiazem HCl XR 240 mg Capsules.

II. Background:

Diltiazem HCl is a calcium ion influx inhibitor. It is well-absorbed from the gastrointestinal tract, and is subject to an extensive first-pass effect. When given as an immediate release oral formulation, the absolute bioavailability of diltiazem is approximately 40%. Diltiazem undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the

urine. The plasma elimination half-life of diltiazem is approximately 3 to 4.5 hours. The apparent steady-state half-life of diltiazem following once-daily administration of Diltiazem Extended-Release Capsules ranges from 5 to 10 hours. This prolongation of half-life is attributed to continued absorption of diltiazem rather than to alterations in its elimination. Diltiazem is metabolized by three major pathways into various metabolites. These pathways are i) O-demethylation, ii) Desacetylation (DAD) and N-monodemethyldiltiazem (NMD). Desacetyldiltiazem and N-monodemethyldiltiazem are active metabolites. At one time, Desacetyldiltiazem was thought to be the major metabolite of diltiazem, which is also present in the plasma at concentrations of 10% to 20% of the parent drug. It is approximately 25% to 50% as potent a coronary vasodilator as diltiazem. There is a departure from linearity when dose strengths are increased; the half-life is slightly increased with dose.

Diltiazem HCl is commercially available as oral tablets, extended-release capsules, and dual-release capsules. Each extended-release diltiazem HCl capsule (Dilacor XR^R, Rhone-Poulenc Rorer) consists of multiple 60-mg tablets contained in a swellable matrix core that slowly releases the drug over approximately 24 hours.

Simultaneous administration of Dilacor XR^R with a high-fat breakfast had a modest effect on diltiazem bioavailability with AUC increasing by 13% and Cmax by 37%. Therefore, Dilacor XR^R Capsules should be taken on empty stomach. Dosage must be adjusted to each patient's needs, starting with 180 mg or 240 mg once-daily.

III. Project/Protocol #P95-166 For Single-dose Fasting Bioequivalence Study:

Study site:	#4 - Confidential business
Analytical site:	
Statistical Analysis:	
Study design:	A randomized, single-dose, open-label, 2-way crossover bioequivalence study under fasting conditions.
Study dates:	Period I, August 12-14, 1995

Period II, August 19-21, 1995

Subjects: Thirty-two (30 + 2 alternates) male volunteers were enrolled in the study. All met the selection and exclusion criteria described in the protocol. They were judged to be healthy based on medical history, physical examination and clinical laboratory tests within 14 days prior to period 1 dosing. All subjects were within 18 to 45 years of age and the weight range was not more than ± 10% for height and body frame as per Desirable Weights for Men - 1983 Metropolitan Height and Weight Table.

Dose and treatment: All subjects completed an overnight fast (10 hours) before any of the following drug treatments:

Test product: A. 1x240 mg Diltiazem HCl Extended-Release (XR) Capsules (Andrx), lot #550R004A, lot size [redacted]#4 - [redacted] Exp. 5/97. Content uniformity and potency are 100.2% (%CV=0.7) and 98.8%, respectively.

Reference product: B. 1x240 mg Dilacor XR® Capsules (Rhone-Poulenc Rorer), lot #L94610, Exp. 9/95. Content uniformity and potency are 100.0% (%CV=2.6) and 97.3%, respectively.

Food and fluid intake: Following drug administration, the subjects remained fasting for 4 hours and then received a meal. Standard meals or snacks were provided at appropriate times thereafter. Meal plans were identical for both periods. Water was permitted ad lib. until 1 hour before dosing and 2 hours after dosing. All subjects consumed 240 mL of water two hours after dosing.

Blood collection: Blood samples (15 mL) were drawn into Vacutainers prior to drug administration. Similarly, 1x15 mL samples were drawn at the following times after dosing: 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36 and 48 hours. All blood samples were drawn at 1 minute intervals. Blood samples were centrifuged at 2400 RPM for 15 minutes. Plasma samples were stored at -70°C until shipment.

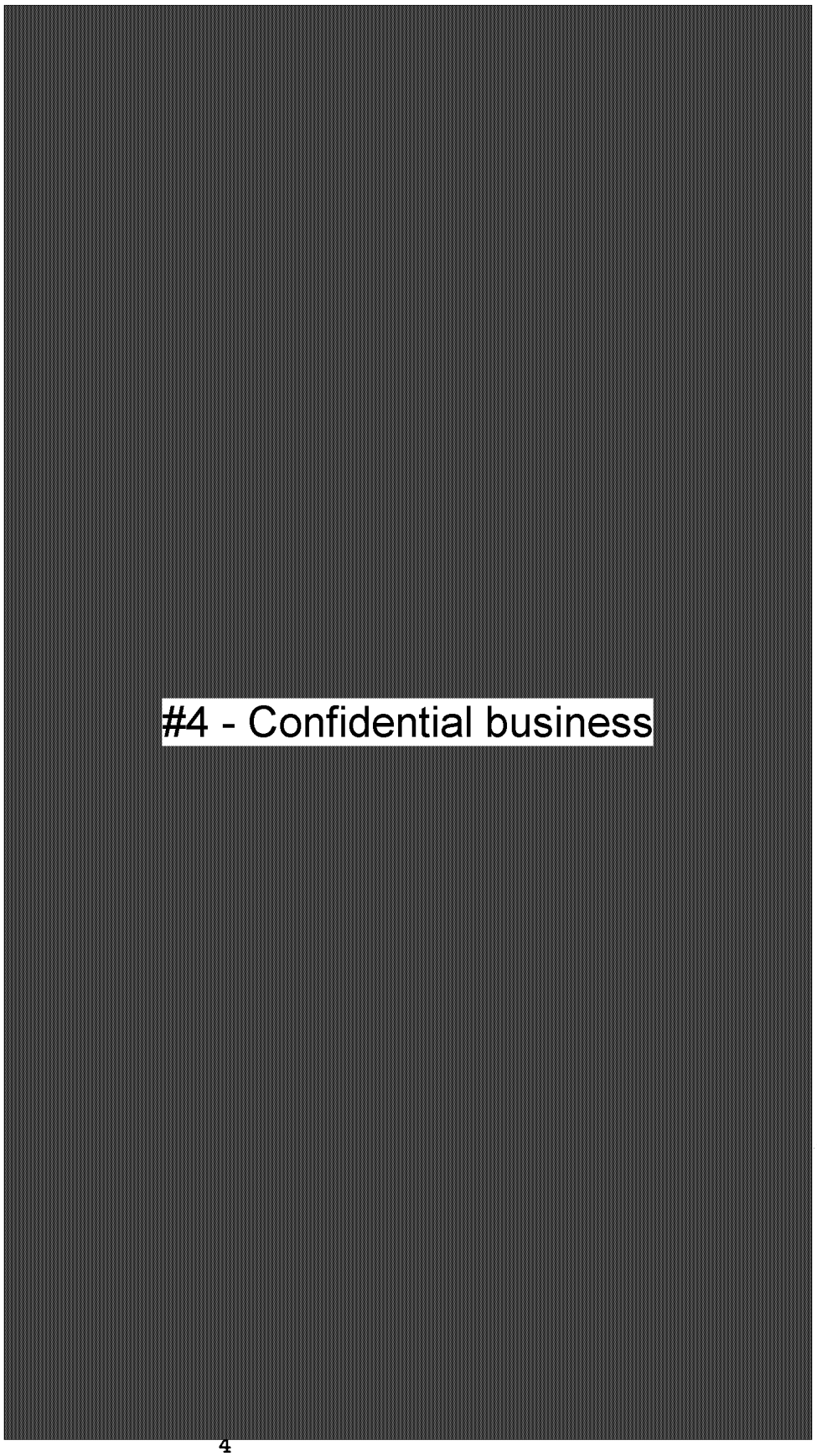
Washout period: One week.

Assay Methodology:

Sensitivity:

Specificity:

Precision:



Accuracy:

Linearity:

Stability:

#4 - Confidential business

Statistical Analysis:

AUCTLQC, AUCinf, Cmax, Kel, T1/2 and concentrations at each sampling time point were determined for diltiazem, desacetyldiltiazem and desmethyldiltiazem. ANOVA was performed at alpha level of 0.05 using the GLM procedure of SAS. The 90% confidence intervals were calculated for LNAUCTLQC, LNAUCinf and LNCmax.

IV. In Vivo Results:

Thirty-two (32) subjects (30 plus two alternates) enrolled in the study. Twenty-eight (28) subjects completed the study. Subjects # 7, 15 and 18 failed to report for period II check-in. Subject #20 dropped prior to period II dosing secondary to an illness. Statistical analysis was performed on all 28 subjects who completed the study. Thirty adverse events were reported in fourteen of the thirty-two subjects dosed over the course of the study. The adverse events are summarized in Table I. Of the thirty reported adverse events, fifteen were probably or possibly related to the study drug. In the opinion of the investigators, the remaining fifteen reported adverse events were remotely or unrelated to the study drug. None of the adverse events was considered serious or resulted in dropping any subject from the study participation.

The plasma concentrations and pharmacokinetic parameters for diltiazem, desacetyldiltiazem and desmethyldiltiazem are summarized below.

Table II

Mean Plasma Diltiazem Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 240 Diltiazem HCl XR Capsule under Fasting Conditions

(N=28)

Time hr	Treatment A Andrx-Test Lot #550R004A ng/mL (CV)	Treatment B Rhone-Poulenc-Reference Lot #L94610 ng/mL (CV)
0	0	0
1	0.96 (223)	11.60 (83.3)
2	18.73 (77.4)	38.82 (58.2)
3	38.04 (56.3)	55.04 (41.3)
4	44.16 (45.5)	61.24 (38.3)
6	50.26 (38.9)	62.21 (33.5)
8	48.12 (29.3)	56.21 (39.9)
10	51.45 (30.5)	52.27 (39.5)
12	62.46 (42.9)	57.83 (45.0)
16	63.41 (41.4)	58.33 (46.6)
20	49.63 (46.2)	48.22 (39.7)
24	47.77 (50.8)	43.62 (37.5)
30	32.27 (52.8)	26.69 (48.5)
36	15.16 (62.7)	10.82 (64.9)
48	4.87 (97.5)	3.23 (139)

			90% CI
AUCTLQC (ng.hr/mL)	1656.60 (38.6)	1623.61 (34.6)	
AUCINf (ng.hr/mL)	1726.51 (38.6)	1675.03 (34.6)	
Cmax (ng/mL)	72.29 (35.1)	73.68 (36.3)	
Tmax (hr)	12.86	8.82	
Kel (1/hr)	0.11	0.125	
T1/2 (hr)	7.23	6.15	
LnAUCTLQC			89.4-115.0%
LnAUCI			90.4-116.0%
LnCmax			87.5-111.0%

1. For Diltiazem, the least squares means for AUCTLQC, AUCI and Cmax values were 2.0%, 3.0% higher and 1.9% lower, respectively, for the test product than for the reference product. The differences are not statistically significant and the 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data. The reviewer's calculations are same as those submitted by the firm.

2. The Diltiazem mean plasma levels for the reference product exhibited higher values than the test values from 1 to 4 hours which may reflect faster drug release from the reference than the test product.

3. The Diltiazem mean plasma levels peaked at 16 and 6 hours for the test and the reference products, respectively, following their administration under fasting conditions.

4. A 46% difference between products for Tmax was detected by ANOVA as statistically significant.

Table III

Mean Plasma Desacetyldiltiazem Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 240 Diltiazem HCl XR Capsule under Fasting Conditions
(N=28)

Time hr	Treatment A Andrx-Test Lot #550R004A ng/mL(CV)	Treatment B Rhone-Poulenc-Reference Lot #L94610 ng/mL(CV)
0	0	0
1	0	0
2	0.08 (529)	0.67 (163)
3	0.90 (156)	2.33 (69.5)
4	2.00 (85.0)	3.62 (38.2)
6	4.08 (42.0)	5.12 (36.3)
8	4.81 (39.9)	5.72 (38.0)
10	5.78 (50.0)	6.21 (43.3)
12	6.98 (67.9)	6.80 (54.9)
16	8.82 (83.5)	8.14 (71.8)
20	9.15 (93.9)	8.81 (74.1)
24	9.83 (104)	9.14 (80.6)
30	8.85 (120)	8.27 (124)
36	5.83 (134)	5.03 (167)
48	1.75 (239)	1.37 (287)

			90% CI
AUCTLQC (ng.hr/mL)	276.82 (109)	265.45 (98)	
AUCINf (ng.hr/mL)	360.48 (100)	327.15 (95)	
Cmax (ng/mL)	10.52 (96)	10.54 (97)	
Tmax (hr)	21.21	22.29	
Kel(1/hr)	0.064	0.075	
T1/2(hr)	13.66	10.34	
LnAUCTLQC			88.9-112.6%
LnAUCI			97.3-117.6%

LnCmax 89.3-109.5%

1. For Desacetyldiltiazem, the least squares means for AUCTLQC and AUCI values were 4.3% and 10.2% higher, respectively, for the test product than for the reference product. The differences are not statistically significant. The Cmax value for the test product was the same as the Cmax value for the reference product. The 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data. The reviewer's calculations are same as those submitted by the firm.

2. The Desacetyldiltiazem plasma levels peaked at 24 hours for both the test and the reference products, following their administration under fasting conditions.

Table IV

Mean Plasma Desmethyldiltiazem Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 240 Diltiazem HCl XR Capsule under Fasting Conditions
(N=28)

Time hr	Treatment A Andrx-Test Lot #550R004A ng/mL(CV)	Treatment B Rhone-Poulenc-Reference Lot #L94610 ng/mL(CV)
0	0	0
1	0.07 (529)	2.09 (83.7)
2	3.89 (82.9)	8.48 (44.1)
3	9.24 (45.7)	14.13 (33.8)
4	12.50 (36.2)	17.62 (33.1)
6	17.43 (35.6)	21.12 (29.0)
8	17.91 (23.8)	20.90 (29.1)
10	18.98 (23.7)	20.58 (30.2)
12	21.58 (27.4)	21.92 (34.3)
16	23.18 (28.8)	22.61 (35.5)
20	20.10 (29.7)	20.58 (32.6)
24	18.99 (32.0)	18.71 (29.7)
30	15.83 (35.0)	14.40 (31.7)
36	10.00 (40.8)	8.31 (40.0)
48	4.15 (55.3)	3.11 (74)

			90% CI
AUCTLQC (ng.hr/mL)	681.24 (25.2)	683.43 (27.4)	
AUCINf (ng.hr/mL)	752.59 (25.3)	740.58 (26.5)	
Cmax (ng/mL)	24.85 (26.6)	25.13 (29.4)	
Tmax (hr)	15.36	12.21	
Kel(1/hr)	0.075	0.08	

T1/2(hr)	10.18	9.03	
LnAUCTLQC			90.8-110.6%
LnAUCI			93.0-111.6%
LnCmax			90.1-109.4%

1. For Desmethyldiltiazem, the least squares means for AUCTLQC and Cmax values were 0.3% and 1.1% higher lower, respectively, for the test product than for the reference product. The differences are not statistically significant and the 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data. The reviewer's calculations are same as those submitted by the firm.

2. The Desmethyldiltiazem plasma levels peaked at 16 hours for both the test and the reference products following their administration under fasting conditions.

V. Study #P95-167, Multiple-dose Bioequivalence Study of Diltiazem HCl 240 mg XR Capsules

The objective of the study was to assess the bioavailablity at steady-state of Diltiazem HCl 240 mg XR Capsules (Andrx) as compared to Dilacor XR® 240 mg Capsules (Rhone-Poulenc Rorer Pharmaceuticals Inc.) following once-a-day dosing of each formulation for five days.

Study site:

Analytical site:

#4 - Confidential business

Statistical Analysis:

Study design: A randomized, multiple-dose, 2-way crossover bioequivalence study under fasting conditions.

Study dates: Period I, September 9-14, 1995
Period II, September 23-28, 1995

Subjects: Twenty-six (26) healthy male volunteers were enrolled in the study. Subjects were within

18 to 45 years of age, the weight range was not more than ± 10% for height and body frame as per Desirable Weights for Men - 1983 Metropolitan Height and Weight Table. All subjects completed an acceptable medical history, physical examination, an electrocardiogram, screens for HIV 1 & 2 antibody, hepatitis B surface antigen and drugs of abuse prior to study initiation. Selected routine clinical laboratory measurements were performed during screening and at the end of the trial. Upon completion of the study, the physical examination was repeated. All subjects met the selection and exclusion criteria described in the protocol. Twenty-four (24) subjects completed the study.

Dose and treatment: All subjects completed an overnight fast (10 hours) prior to dose administration until at least 4 hours after dosing during each study period.

Test product: A. Days 1-5: 1x240 mg Diltiazem HCl Extended-Release (XR) Capsules (Andrx), lot #550R004A, lot size [redacted] #4 - [redacted] Exp. 5/97. Content uniformity and potency are 100.2% (%CV=0.7) and 98.8%, respectively. The single oral dose was administered with 240 mL of water at 8 AM following a 10 hour overnight fast.

Reference product: B. Days 1-5: 1x240 mg Dilacor XR^{R} Capsules (Rhone-Poulenc Rorer), lot #L94610, Exp. 9/95. Content uniformity and potency are 100.0% (%CV=2.6) and 97.3%, respectively. The single oral dose was administered with 240 mL of water at 8 AM following a 10 hour overnight fast.

Blood collection: Blood samples were drawn into Vacutainers within one hour prior to Dose 1 (0 hour) and after Dose 1 at 24 , 48, 72, 96, 97, 98, 99, 100, 102, 104, 106, 108, 112, 116, and 120 hours. Blood samples were centrifuged at 2400 RPM for 15 minutes. Plasma samples were stored at -70^{0}C until shipment for analysis.

Subjects monitoring: The subjects were monitored throughout the confinement portion of the study. Blood pressure and heart rate were obtained prior to dosing and at 3, 5, 7, 12, 24, 36, 48, 72,

84, 96, 108 and 120 hours after Dose 1. Electrocardiograms were recorded at check-in, 6 hours after each dose and prior to discharge from the clinical study unit.

Washout period: One week.

Assay Methodology: Same as Study #P95-166 above.

Statistical Analysis:

AUC_{0-T}, Cmax, Cmin, Tmax, Flux and concentrations at each sampling time point were determined for diltiazem, desacetyldiltiazem and desmethyldiltiazem. ANOVA was performed at alpha level of 0.05 using the GLM procedure of SAS. The 90% confidence intervals were calculated for $LNAUC_{0-T}$ and LNCmax.

VI. In Vivo Results:

Twenty-six (26) subjects enrolled in the study. Twenty-four (24) subjects completed the study. Subjects #22 elected to withdraw prior to Dose-1 for period I. Subject #16 left the evening of study Day 4, period I against medical advice for personal reasons. Ten adverse events were reported in five of the twenty-five subjects dosed and included the following events: cough (1), headache (6), malaise (1 - body ache), pharyngitis (1 - sore throat), and respiratory disorder (1 - nasal congestion). Of the ten reported adverse events, seven were probably or possibly related to the study drug. In the opinion of the investigators, the remaining three reported adverse events were remotely or unrelated to the study drug. None of the adverse events was considered serious or resulted in dropping any subject from the study participation.

The plasma concentrations and pharmacokinetic parameters for diltiazem, desacetyldiltiazem and desmethyldiltiazem are summarized below.

Table V

Mean Diltiazem Plasma Concentrations and Pharmacokinetic Parameters Following a Multiple Dosing (5x240 mg) of Diltizem HCl XR Capsules
(N=24)

Time hr	Treatment A Andrx-Test Lot #550R004A ng/mL(CV)	Treatment B Rhone-Poulenc-Reference Lot #L94610 ng/mL(CV)
0	0.00	0.00
24	43.57 (53.2)	40.44 (42.6)
48	57.18 (46.7)	48.14 (58.3)
72	58.80 (35.9)	48.18 (52.7)
96	57.20 (42.1)	46.16 (43.6)
97	61.05 (45.5)	65.01 (40.0)
98	97.36 (42.4)	102.79 (34.8)
99	116.60 (35.9)	119.32 (31.9)
100	112.98 (36.9)	123.64 (30.3)
102	114.88 (34.7)	114.56 (34.8)
104	98.92 (34.0)	96.16 (30.9)
106	85.17 (36.0)	77.90 (28.9)
108	87.09 (33.3)	71.82 (25.4)
112	84.68 (31.2)	66.96 (33.9)
116	65.50 (40.2)	50.16 (37.2)
120	62.60 (53.1)	46.36 (47.2)

			90% CI
AUC(0-24)(ng.hr/mL)	2073.2 (32.7)	1849.6 (29.1)	
Cmax (ng/mL)	131.7 (33.6)	128.6 (31.5)	
Cmin(C96) (ng/mL)	57.2 (42.0)	46.2 (43.6)	
Tmax (hr)	5.4	4.6	
Css (ng/mL)	86.4 (32.7)	77.1 (29.1)	
Fluct (%)	88.9 (30.9)	108.4 (18.2)	
LnAUC(0-24)			105.8-115.2%
LnCmax			94.2-109.2%

1. The plasma Diltiazem levels peaked at 99 and 100 hours for the test and the reference products, respectively.

2. For diltiazem, the least squares means for AUC(0-24) and Cmax values were 11.8% and 2.5% higher, respectively, for the test product than for the reference product. The difference between products for AUC(0-24) was detected by ANOVA as statistically significant. The 90% confidence intervals for each of the above parameters are within the acceptable range of 80-125%.

Table VI

Mean Desacetyldiltiazem Plasma Concentrations and Pharmacokinetic Parameters Following a Multiple Dosing (5x240 mg) of Diltizem HCl XR Capsules
(N=24)

Time hr	Treatment A Andrx-Test Lot #550R004A ng/mL(CV)	Treatment B Rhone-Poulenc-Reference Lot #L94610 ng/mL(CV)
0	0.12 (489)	0.28 (490)
24	10.92 (84.7)	10.68 (80.7)
48	17.93 (127)	17.27 (122)
72	21.52 (142)	17.73 (135)
96	20.39 (135)	18.51 (130)
97	20.83 (139)	19.94 (133)
98	21.82 (128)	21.46 (129)
99	23.49 (133)	22.93 (125)
100	24.43 (129)	24.00 (127)
102	25.57 (128)	25.62 (127)
104	24.50 (130)	24.11 (126)
106	23.56 (127)	23.31 (129)
108	23.19 (127)	21.76 (123)
112	23.53 (124)	22.35 (126)
116	21.89 (126)	19.89 (135)
120	22.61 (140)	18.39 (135)

			90% CI
AUC(0-24)(ng.hr/mL)	556.7 (128)	526.7 (128)	
Cmax (ng/mL)	26.8 (123)	26.5 (122)	
Cmin(C96) (ng/mL)	20.3 (135	18.5 (130)	
Tmax (hr)	10.2	7.4	
Css (ng/mL)	23.2 (128)	21.9 (128)	
Fluct (%)	30.6 (47)	41.0 (43.6)	
LnAUC(0-24)			99.9-111.5%
LnCmax			94.2-107.5%

1. The plasma Desacetyldiltiazem levels peaked at 102 hours for both the test and the reference products.

2. For Desacetyldiltiazem, the least squares means for AUC(0-24) and Cmax values were 5.8% and 0.5% higher, respectively, for the test product than for the reference product. The differences were not statistically significant. The 90% confidence intervals for each of the above parameters are within the acceptable range of

80-125%.

Table VII

Mean Desmethyldiltiazem Plasma Concentrations and Pharmacokinetic Parameters Following a Multiple Dosing (5x240 mg) of Diltizem HCl XR Capsules
(N=24)

Time hr	Treatment A Andrx-Test Lot #550R004A ng/mL(CV)	Treatment B Rhone-Poulenc-Reference Lot #L94610 ng/mL(CV)
0	0.00	0.00
24	19.73 (35.4)	18.56 (32.3)
48	26.18 (33.8)	24.49 (37.5)
72	28.14 (30.0)	24.39 (36.6)
96	27.43 (29.6)	24.05 (32.6)
97	27.92 (32.2)	26.65 (30.3)
98	33.58 (29.3)	33.85 (27.1)
99	38.20 (26.8)	38.09 (22.9)
100	40.81 (27.0)	40.45 (25.5)
102	43.02 (27.4)	42.50 (26.5)
104	41.48 (26.8)	40.73 (24.6)
106	38.92 (27.1)	37.17 (22.6)
108	38.41 (25.7)	35.18 (20.8)
112	38.33 (24.2)	33.43 (26.7)
116	31.87 (29.6)	26.47 (31.1)
120	30.05 (35.2)	23.77 (33.7)

			90% CI
AUC(0-24)(ng.hr/mL)	877.6 (25.6)	804.7 (23.8)	
Cmax (ng/mL)	45.4 (24.7)	44.3 (24.5)	
Cmin(C96) (ng/mL)	27.4 (29.6)	24.1 (32.6)	
Tmax (hr)	7.6	6.0	
Css (ng/mL)	36.6 (25.6)	33.5 (23.8)	
Fluct (%)	50.2 (31.9)	61.0 (24.4)	
LnAUC(0-24)			104.2-112.3%
LnCmax			96.9-108.2%

1. The plasma Desmethyldiltiazem levels peaked at 102 hours for both the test and the reference products.

2. For Desmethyldiltiazem, the least squares means for AUC(0-24) and Cmax values were 8.8% and 2.3% higher, respectively, for the test product than for the reference product. The difference

between products for AUC(0-24) was detected by ANOVA as statistically significant. The 90% confidence intervals for each of the above parameters are within the acceptable range of 80-125%.

VII. Study #P95-165 For Single-dose Post Prandial Bioequivalence Study of Diltiazem HCl 240 mg XR Capsules

The objective of this study was to evaluate the effect of food on the rate and extent of absorption of a single dose of Diltiazem HCl XR 240 mg Capsules (Andrx) relative to Dilacor XR® 240 mg Capsules (Rhone-Poulenc Rorer Pharmaceuticals Inc.)

Study site:	#4 - Confidential business
Analytical site:	
Statistical Analysis:	
Study design:	Single-dose, three-way crossover, post-prandial bioequivalence study.
Study dates:	Period I, August 5-7, 1995 Period II, August 12-14, 1995 Period III, August 19-21, 195
Subjects:	Twenty-four (24) healthy male volunteers were enrolled in the study. All met the selection and exclusion criteria described in the protocol. There was one dropout (subject #9) over the course of the study who was not replaced.
Dose and treatment:	All subjects completed an overnight fast (10 hours) before any of the following drug treatments:
Test product:	A. 1x240 mg Diltiazem HCl Extended-Release (XR) Capsules (Andrx), lot #550R004A, administered following an overnight fast.

B. 1x240 mg Diltiazem HCl Extended-Release (XR) Capsules (Andrx), lot #550R004A, administered within 30 minutes of a high fat breakfast preceded by an overnight fast.

Reference product: B. 1x240 mg Dilacor XR^R Capsules (Rhone-Poulenc Rorer), lot #L94610, administered within 30 minutes of a high fat breakfast preceded by an overnight fast.

Food and fluid intake: Following drug administration, the subjects remained fasting for 4 hours and then received a meal. Standard meals or snacks were provided at appropriate times thereafter. Meal plans were identical for both periods. No fluid except that given with the standardized breakfast (1 fried egg, 1 serving of hashed browned potatoes, 1 slice Canadian bacon, 1 buttered English muffin, 1 slice American cheese, 8 ounces of whole milk and 6 ounces of orange juice) and with drug administration was allowed from 1 hour prior to dose administration until 2 hours after dosing. At 2 hours post-dose, all subjects consumed 240 mL of water. Four hours after dose, water was allowed ad lib, if requested, but was generally controlled during confinement and limited to approximately 4500 mL from the time of dosing until release from the study site.

Blood collection: Blood samples (15 mL) were drawn into Vacutainers prior to drug administration. Similarly, 1x15 mL samples were drawn at the following times after dosing: 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36 and 48 hours. All blood samples were drawn at 1 minute intervals. Blood samples were centrifuged at 2400 RPM for 15 minutes. Plasma samples were stored at -70^{0}C until shipment.

Washout period: One week.

Assay Methodology: Same as Study #P95-166 above.

Statistical Analysis

Cmax for diltiazem, desacetyldiltiazem and desmethyldiltiazem was determined by establishing the peak concentration for each subject. The areas under the plasma diltiazem, desacetyldiltiazem

and desmethyldiltiazem concentration versus time curves (AUCs) were calculated by using the linear trapezoidal rule.

VIII. In Vivo Results:

Twenty-four (24) subjects enrolled in the study. Twenty-three (23) subjects completed the study. Subject #9 elected to withdraw from study participation prior to period III dosing for personal reasons. The urine drug abuse screen was negative for all subjects.
Statistical analysis was performed on all 23 subjects who completed the study. Thirty-seven adverse events were reported in eighteen of the twenty-three subjects dosed and included the following events: headache (24), abdominal pain (2), dizziness (2), upset stomach (1), rhinitis (2), purpura (3) and pain (3, neck tension, left knee, right knee). Of the thirty-seven reported adverse events, twenty-five (25) were probably or possibly related to the study drug. In the opinion of the investigators, the other twelve adverse events were either remotely or unrelated to the study drug. None of the adverse events was considered serious or resulted in dropping any subject from the study participation.

The following exit clinical chemistry values were outside the reference range and deemed not clinically significant by the medical investigator.

Subject No.	Laboratory Parameter	Laboratory result	
6	SGPT	42	H
9	Creatinine	1.5	H
9	BUN	20.9	H
10	Creatinine	1.5	H
10	Total Protein	8.4	H
14	Total Bili	1.1	H
15	SGPT	42	H
17	SGOT	36	H
17	SGPT	101	H

Subject #17 had a high value for SGPT (101 u/l) at the end of the study. The normal values for SGPT range from 4 to 37 u/l. According to the CRF of subject 17, his SGPT values which were monitored before and after the study were as follows:

Date	Period	Treatment	SGPT value
8/2/95	screening	before study	34
8/5/95	I	Test Product-Fasting	Not available
8/12/95	II	Reference Product-Fed	Not available
8/19/95	III	Test Product-Fed	Not available
8/21/95	---	After study	101

8/23/95	Follow-up	113
10/5/95	Follow-up	70
10/26/95	Follow-up	51

The firm indicated that upon follow-up with subject 17, the investigator discovered the subject had consumed alcohol prior to collection of the exit clinical laboratories. The alcohol consumption was in violation of the protocol instructions. For this and potential effect of alcohol consumption of study data, the firm requested to exclude subject #17 from the data analysis.

The plasma concentrations and pharmacokinetic parameters for diltiazem, desacetyldiltiazem and desmethyldiltiazem are summarized below.

Table VIII

Mean Plasma Diltiazem Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 240 Diltiazem HCl XR Capsule under Fasting and Nonfasting Conditions
(N=23)

Time hr	Treatment A Andrx-Test Lot #550R004A Fasting ng/mL(CV)	Treatment B Andrx-Test Lot #550R004A Nonfasting ng/mL(CV)	Treatment C Rhone-Poulenc-Reference Lot #L94610 Nonfasting ng/mL
0	0	0	0
1	1.80 (218)	0	0.41 (348)
2	26.66 (80.9)	13.72 (238)	15.02 (63.2)
3	44.31 (45.0)	39.49 (144)	44.75 (51.2)
4	46.57 (36.4)	77.30 (89.7)	59.14 (43.4)
6	51.07 (33.6)	143.93 (56.3)	87.37 (40.2)
8	58.22 (49.9)	121.73 (47.4)	101.28 (53.3)
10	67.98 (66.6)	107.28 (45.0)	105.61 (45.9)
12	83.19 (68.7)	104.61 (43.5)	95.83 (45.5)
16	75.92 (63.9)	80.87 (35.2)	77.82 (43.6)
20	62.03 (58.8)	56.87 (32.9)	68.93 (34.7)
24	53.10 (55.6)	45.37 (39.2)	61.41 (40.9)
30	30.34 (49.6)	21.66 (47.7)	27.34 (53.5)
36	13.20 (59.5)	9.44 (61.7)	11.53 (61.3)
48	4.51 (133)	2.43 (108)	2.98 (114)

	A	B	C	B/C
AUCTLQC (ng.hr/mL)	1882.43(49.8)	2221.81(40.6)	2187.96(35.8)	1.02
AUCINf (ng.hr/mL)	1940.40(49.6)	2262.44(40.5)	2231.94(35.9)	1.01
Cmax (ng/mL)	93.26(58.0)	156.40(49.0)	120.04(42.2)	1.30

Tmax (hr)	13.26	7.65	11.73
Kel(1/hr)	0.12	0.12	0.13
T1/2(hr)	5.77	5.88	5.55

1. The diltiazem mean plasma levels peaked at 6 and 10 hours for the test and reference products, respectively, under nonfasting conditions and at 12 hours for the test product under fasting conditions.

2. For Andrx's test product, the mean AUCTLQC, AUCinf and Cmax values were 1.5%, 1.4% and 30.3% higher, respectively, than the reference product values under nonfasting conditions. The ratios of the test arithmetic mean to the reference arithmetic mean are within the acceptable range of 0.8-1.2 for AUCTLQC and AUCinf. The ratio of the test arithmetic mean to the reference arithmetic mean is 1.3 for Cmax, which is outside the acceptable range of 0.8-1.2 under nonfasting conditions.

3. For the test product, the mean AUCTLQC, AUCINF and Cmax values after dosing with food were about 118%, 117% and 167%, respectively, of the values reported in the fasting state.

4. For the Test product under nonfasting conditions, the firm indicated that subject #6 exhibited a high Cmax value of 353 ng/mL versus a mean Cmax value of 156 ng/mL for diltiazem (DTM). The pharmacokinetic parameters values for subjects #6 and #17 are:

Subject	Treatment A		Treatment B			Treatment C	
No	Period	Andrx-Test fasting	Period	Andrx-Test Nonfasting	Period	Poulenc Nonfasting	
		AUCT Cmax		AUCT Cmax		AUCT	Cmax
6	1	4057 233	2	4309 353	3	3809	165
17	1	2601 94	3	4411 343	2	4058	187

Since subjects #6 and #17 have average levels of metabolites desacetyldiltiazem (DAD) and N-monodemethyldiltiazem (NMD). The firm indicated that the high DTM Cmax/DAD Cmax and DTM Cmax/NMD Cmax ratios and the high ratios of the corresponding AUCT are a reflection of the high Cmax value of diltiazem in subject #6. These high ratios suggest an unusual decrease in metabolism of diltiazem to produce DAD and NMD by the liver for that treatment period (the Test product under nonfasting conditions for subject #6, period II). Additionally, the firm claims the nonlinear pharmacokinetic property of diltiazem contributes to the high variability of Cmax and AUC, especially when the AUC value is large. The firm requested excluding subject #6 from the statistical analysis of the study.

The ratios of DTM Cmax/DAD Cmax and DTM Cmax/NMD Cmax and the

corresponding AUCT ratios for subject #6, period III (the Reference product under nonfasting conditions) are similar as some subjects treated with reference product. The firm's arguments of decrease in the metabolism of diltiazem for subject #6 only in period II (Test product) are not scientifically strong reasons to eliminate the subject from the statistical analysis of the study.

5. Subject #17 had a value of 101 u/l for SGPT at the end of the study. The firm claims that this high value probably occurred during the period when the test product was being evaluated, since this value was obtained only two days after dosing of the test product under nonfasting conditions. The high value of SGPT is an indication of liver dysfunction which may be responsible for the unusually high Cmax value (343 ng/mL) for subject #17. In addition, upon follow-up with subject #17, it was discovered that subject #17 had consumed alcohol prior to collection of the exit clinical laboratories which might have had potential effect on the study data. Based on the SGPT value and the consumption of alcohol, the firm requested excluding subject #17 from the statistical analysis of the study.

However, the high value of SGPT in itself is not a definite indication of liver injury or liver dysfunction. The SGPT value increased from 101 u/l on 8/21/95 (at the end of the study) to 113 u/l on 8/23/95 (at follow up). The sustained high values of SGPT (please see SGPT values for subject 17 before and after the study above) might have been result of liver injury, in addition to the consumption of alcohol. Therefore, excluding subject #17 from the statistical analysis of the study is justified.

After excluding subject #17 from the statistical analysis of the study, the ratios of the arithmetic and geometric means for Diltiazem are as following:

	B/C Arithmetic Mean	B/C Geometric Mean
AUCTLQC	1.00	0.99
AUCinf	1.00	0.99
Cmax	1.25	1.24

The ratios of the geometric means are within the acceptable range of 0.8-1.25 for AUCTLQC, AUCinf and Cmax.

Table IX

Mean Plasma desacetyldiltiazem Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 240 Diltiazem HCl XR Capsule under Fasting and Nonfasting Conditions
(N=23)

Time hr	Treatment A Andrx-Test Lot #550R004A Fasting ng/mL(CV)	Treatment B Andrx-Test Lot #550R004A Nonfasting ng/mL(CV)	Treatment C Rhone-Poulenc-Reference Lot #L94610 Nonfasting ng/mL
0	0	0	0
1	0	0	0
2	0.20 (331)	0	0
3	1.20 (121)	1.13 (198)	0.99 (129)
4	2.37 (59.3)	2.73 (110)	2.95 (30.7)
6	4.07 (28.8)	7.54 (47.0)	5.56 (25.2)
8	4.92 (30.8)	9.68 (46.3)	7.52 (33.8)
10	6.48 (68.4)	10.45 (48.9)	9.08 (36.8)
12	7.31 (59.9)	10.78 (48.9)	9.60 (39.5)
16	9.02 (65.9)	10.58 (44.7)	9.85 (41.9)
20	9.83 (81.2)	9.72 (40.8)	9.97 (39.7)
24	9.72 (75.5)	8.73 (41.7)	10.01 (35.8)
30	7.84 (99.3)	5.55 (58.6)	6.44 (43.6)
36	4.45 (104)	3.17 (57.4)	3.60 (56.8)
48	1.22 (161)	0.33 (266)	1.26 (200)

	A	B	C	B/C
AUCTLQC (ng.hr/mL)	265.65(80.8)	266.53(48.3)	268.08(41.1)	0.99
AUCINf (ng.hr/mL)	332.40(67.8)	307.88(41.1)	306.44(38.0)	1.00
Cmax (ng/mL)	10.94(25.4)	11.88(42.8)	11.57(35.8)	1.02
Tmax (hr)	21.30	13.82	18.96	
Kel(1/hr)	0.08	0.09	0.08	
T1/2(hr)	9.27	7.87	8.37	

1. The desacetyldiltiazem mean plasma levels peaked at 12 and 24 hours for the test and reference products, respectively, under nonfasting conditions and at 20 hours for the test product under fasting conditions.

2. For Andrx's test product, the mean AUCINF, Cmax and AUCLTQC values were 0.5%, 2.7% higher and 1.5% lower, respectively, than the reference product values under nonfasting conditions. The ratios of the test arithmetic mean to the reference arithmetic mean are within the acceptable range of 0.8-1.2 for AUCTLQC,

AUCinf and Cmax.

3. After excluding subject #17 from the statistical analysis of the study, the ratios of the arithmetic and geometric means for desacetyldiltiazem are as following:

	B/C Arithmetic Mean	B/C Geometric Mean
AUCTLQC	0.99	0.96
AUCinf	0.98	0.97
Cmax	1.01	1.00

The ratios of the geometric means are within the acceptable range of 0.8-1.25 for AUCTLQC, AUCinf and Cmax.

Table X

Mean Plasma desmethyldiltiazem Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 240 Diltiazem HCl XR Capsule under Fasting and Nonfasting Conditions
(N=23)

Time hr	Treatment A Andrx-Test Lot #550R004A Fasting ng/mL(CV)	Treatment B Andrx-Test Lot #550R004A Nonfasting ng/mL(CV)	Treatment C Rhone-Poulenc-Reference Lot #L94610 Nonfasting ng/mL
0	0	0	0
1	0.12 (480)	0	0
2	5.72 (68.7)	2.07 (275)	3.10 (74.0)
3	10.95 (34.6)	8.28 (149)	10.81 (33.4)
4	13.73 (25.9)	17.79 (81.6)	16.51 (24.6)
6	17.81 (24.9)	40.21 (40.1)	28.68 (20.7)
8	19.81 (28.7)	42.18 (37.0)	33.74 (30.9)
10	22.47 (42.0)	39.95 (35.7)	37.54 (28.6)
12	25.82 (43.4)	39.87 (33.1)	37.90 (30.5)
16	27.33 (44.9)	34.34 (28.2)	34.27 (27.8)
20	24.82 (42.9)	27.05 (27.0)	31.25 (25.6)
24	22.26 (44.3)	22.09 (26.3)	28.49 (28.9)
30	17.18 (42.5)	14.92 (31.3)	18.85 (34.7)
36	10.51 (43.0)	8.65 (35.6)	10.82 (39.6)
48	4.39 (64.3)	3.14 (55.9)	3.97 (54.4)

	A	B	C	B/C
AUCTLQC (ng.hr/mL)	775.48(37.0)	939.14(28.7)	984.90(24.3)	0.95
AUCINf (ng.hr/mL)	832.96(36.9)	984.11(28.4)	1037.70(24.9)	0.95
Cmax (ng/mL)	29.46(38.5)	47.00(30.7)	41.81(27.8)	1.12
Tmax (hr)	14.61	8.70	13.39	
Kel(1/hr)	0.085	0.086	0.088	
T1/2(hr)	8.33	8.23	7.98	

1. The desmethyldiltiazem mean plasma levels peaked at 8 and 12 hours for the test and reference products, respectively, under nonfasting conditions and at 16 hours for the test product under fasting conditions.

2. For Andrx's test product, the mean AUCLTQC, AUCINF and Cmax values were 4.6%, 5.2% lower and 12.4% higher, respectively, than the reference product values under nonfasting conditions. The ratios of the test arithmetic mean to the reference arithmetic mean are within the acceptable range of 0.8-1.2 for AUCTLQC, AUCinf and Cmax.

3. After excluding subject #17 from the statistical analysis of the study, the ratios of the arithmetic and geometric means for desmetyldiltiazem are as following:

	B/C Arithmetic Mean	B/C Geometric Mean
AUCTLQC	0.95	0.94
AUCinf	0.94	0.94
Cmax	1.11	1.10

The ratios of the geometric means are within the acceptable range of 0.8-1.25 for AUCTLQC, AUCinf and Cmax.

IX. Formulations:

Andrx's formulations for its Diltiazem HCl XR 240 mg, 180 mg and 120 mg Capsules are shown in Table XI.

X. In vitro Dissolution Testing:

Method: USP 23 apparatus II (paddle) at 100 rpm
Media: Water, SGF, pH 4.2, pH 6.2 and SIF
Number of Capsules: 12
Test Product: Andrx's Diltiazem HCl XR capsules 240 mg, Lot #550R004

180 mg, Lot #549R004
120 mg, Lot #548R003

Reference Product: Rhone-Poulenc's Dilacor^{R} XR Capsules
240 mg, Lot #L94610
180 mg, Lot #L99407
120 mg, Lot #L85912

The dissolution testing results are presented in table XII.

XI. Comments:

1. The firm's single-dose bioequivalence study #P95-166 under fasting conditions, conducted on its 240 mg Diltiazem HCl XR Capsule is acceptable. The 90% confidence intervals for LnAUCTLQC, LnAUCinf and Cmax are within the acceptable range of 80-125% for Diltiazem, Desmethyldiltiazem and Desacetyldiltiazem.

2. The firm's multiple-dose bioequivalence study #P95-167 under fasting conditions, conducted on its 240 mg Diltiazem HCl XR Capsule is acceptable. The 90% confidence intervals for LnAUC(0-24) and Cmax are within the acceptable range of 80-125% for Diltiazem, Desmethyldiltiazem and Desacetyldiltiazem.

3. The firm's single-dose bioequivalence study #P95-165 under fasting and nonfasting conditions, conducted on its 240 mg Diltiazem HCl XR Capsule is acceptable. The ratios of the test geometric mean to the reference geometric mean are within 0.80-1.25 for Diltiazem, Desmethyldiltiazem and Desacetyldiltiazem under nonfasting conditions.

4. In study #p95-165, the firm requested excluding subject #6 and #17 from the statistical analysis of the study.

Subject #6 revealed no clinical abnormalities except a slight elevation in SGPT value of 42 u/l. Subject #6 exhibited a high Cmax value of 353 ng/mL versus a mean Cmax value of 156 ng/mL for diltiazem (DTM) upon treatment with the test product under nonfasting conditions. The firm suggested this Cmax value of subject #6 was a result of an unusual decrease in metabolism of diltiazem to produce DAD and NMD by the liver for that treatment period. Excluding subject #6 from the statistical analysis of the study is not justified.
Subject #17 had a value of 101 u/l for SGPT at the end of the study. The firm claimed that the high value of SGPT is an indication of liver dysfunction which may be responsible for the unusually high Cmax value (343 ng/mL) for subject #17 upon treatment with the test product under nonfasting conditions.
In addition, upon follow-up on subject #17, it was discovered that subject #17 had consumed alcohol prior to collection of the exit clinical laboratories which might have had potential effect on the study data.

Excluding subject #17 from the statistical analysis of the study is justified.

5. It should be noted that after excluding subject 17 from the statistical analysis of the study, the resulted ratio of the test geometric mean to the reference mean geometric for Cmax is 1.24, which is within the acceptable range of 0.80-1.25 for diltiazem under nonfasting conditions.

6. The formulations for Diltiazem HCl XR Capsules, 120 mg and 180 mg are proportionally similar to the 240 mg strength of the test product.

7. The firm conducted dissolution testing on its Diltiazem HCl XR Capsules, 120 mg, 180 mg and 240 mg in water, SGF, pH 4.2, pH 6.2 and SIF. USP 23, supplement #3, page 2919, recommended dissolution specifications for Diltiazem HCl XR Capsules, Test #2 in 900 mL water and Test #3 in 900 mL 0.1N HCl. The test products do not meet USP specifications for Test #2 in water at any time points.

XII. Deficiency Comment:

The firm is advised to submit comparative dissolution profiles on its Diltiazem HCl XR Capsules, 120 mg, 180 mg and 240 mg generated in 900 ml of 0.1N HCl. The dissolution method or methods the firm plans to use along with the proposed dissolution specifications should be submitted in detail.

XIII. Recommendations:

1. The single-dose bioequivalence study #P95-166, conducted by Andrx Pharmaceuticals, Inc., on its Diltiazem HCl Extended Release (XR) 240 mg Capsules, lot #550R004A, comparing it to Dilacor XR^R 240 mg Capsules manufactured by Rhone-Poulenc Rorer has been found acceptable by the Division of Bioequivalence. The study demonstrates that Andrx's Diltiazem HCl XR Capsules, 240 mg is bioequivalent to Rhone-Poulenc Rorer's Dilacor XR^R 240 mg Capsules.

2. The multiple-dose steady-state bioequivalence study #P95-167, conducted by Andrx Pharmaceuticals, Inc., on its Diltiazem HCl Extended Release (XR) 240 mg Capsules, lot #550R004A, comparing it to Dilacor XR^R 240 mg Capsules manufactured by Rhone-Poulenc Rorer has been found acceptable by the Division of Bioequivalence. The study demonstrates that Andrx's Diltiazem HCl XR, Capsules 240 mg is bioequivalent to Rhone-Poulenc Rorer's Dilacor XR^R 240 mg Capsules.

3. The single-dose post-prandial bioequivalence study #P95-165, conducted by Andrx Pharmaceuticals, Inc., on its Diltiazem HCl Extended Release (XR) 240 mg Capsules, lot #550R004A, comparing

it to Dilacor XR® 240 mg Capsules manufactured by Rhone-Poulenc Rorer has been found acceptable by the Division of Bioequivalence. The study demonstrates that Andrx's Diltiazem HCl XR, Capsules 240 mg is bioequivalent to Rhone-Poulenc Rorer's Dilacor XR® 240 mg Capsules.

4. The dissolution testing conducting by Andrx Pharmaceuticals, Inc., on its Diltiazem HCl Extended Release (XR), 240 mg, 180 mg and 120 mg Capsules, lot #550R004, 549R004 and 548R003, respectively, has been found incomplete by the Division of Bioequivalence for the reasons given in deficiency comment.

5. Waivers of the in vivo bioequivalence study requirements for the firm's Diltiazem HCl Extended Release (XR), 180 mg and 120 mg Capsules can not be granted for the reasons given in deficiency comment.

The firm should be informed of the deficiency comment and recommendations.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

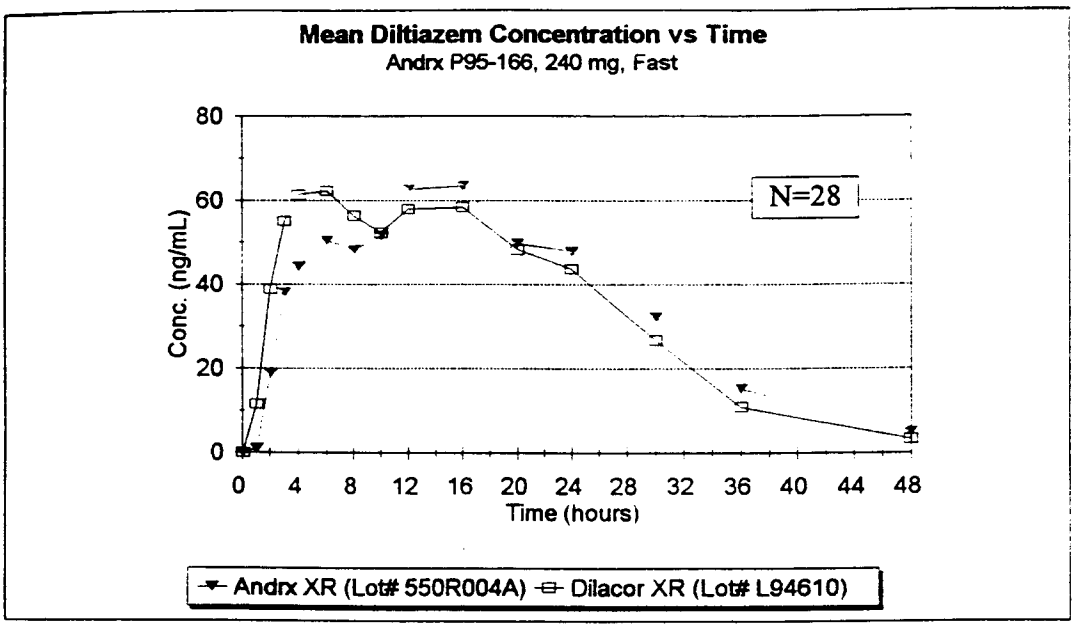
RD INITIALLED RMHATRE /S/ Date: 8/1/96
FT INITIALLED RMHATRE

Concur /S/ Date: 8/5/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

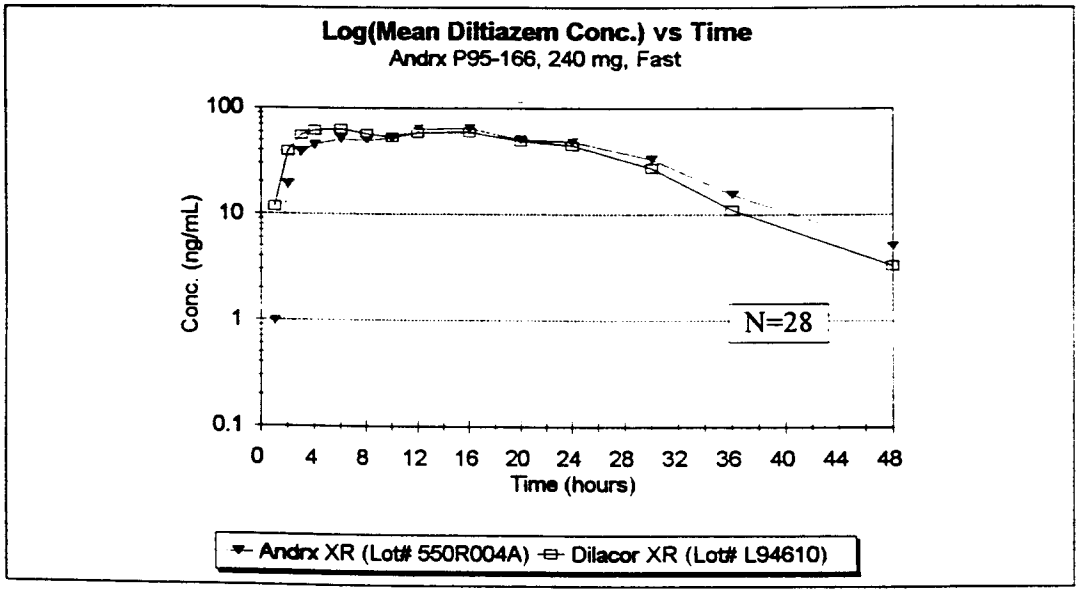
MMakary/8-1-96 wp 74852SDW.D95
cc: ANDA #74-852, original, HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-658 (Mhatre, Makary), Drug File, Division File.

Protocol 95-166 - Single Dose Fasting - Diltiazem

Linear Plot -



Semilog Plot -

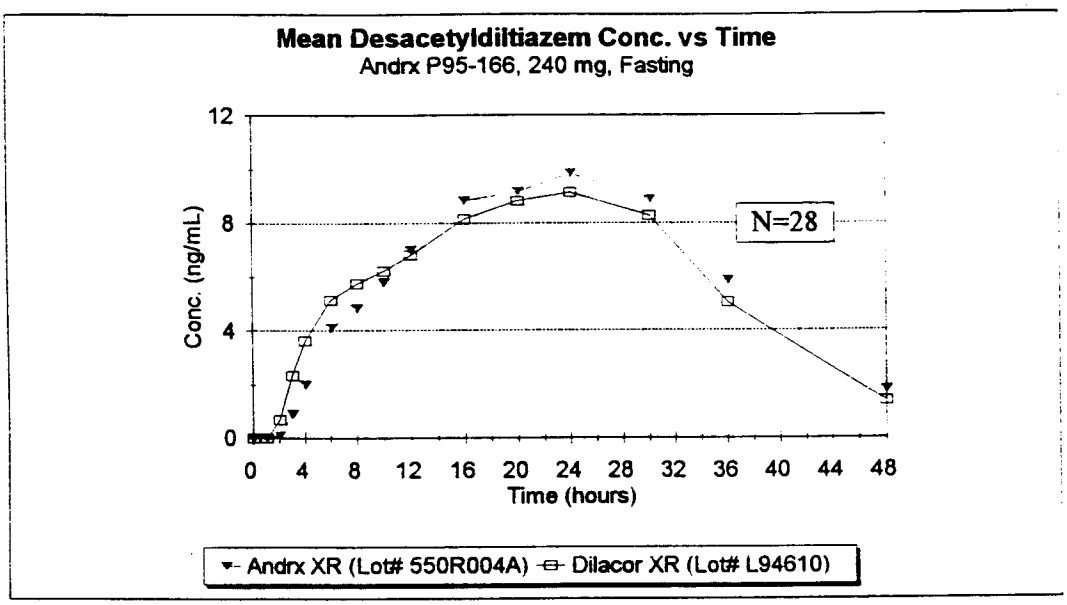


Summary of Test/Reference Ratios (as percents) and 90% Confidence Limits (N=28)

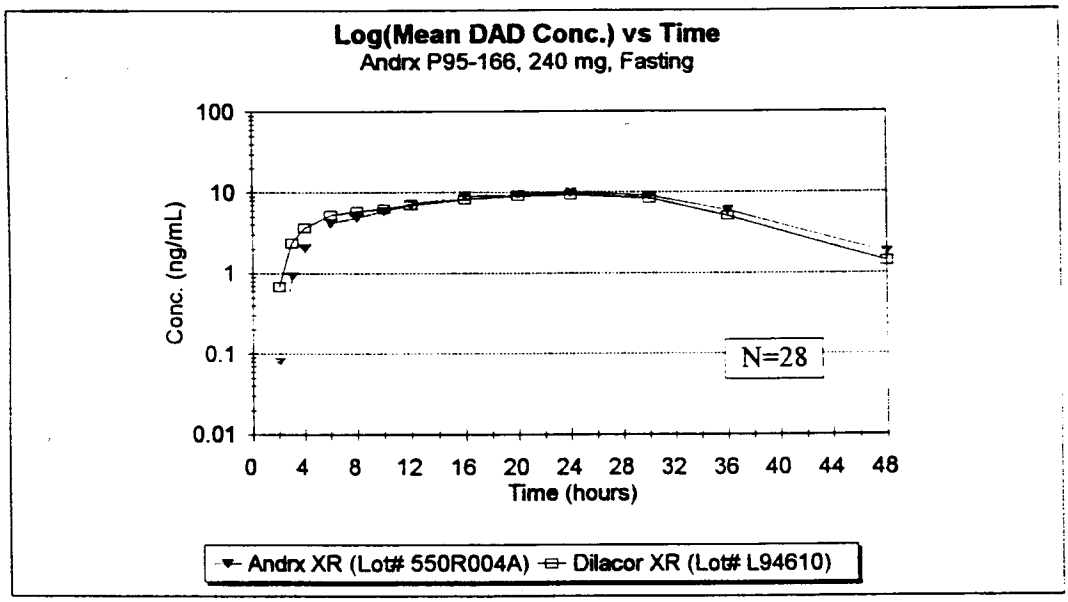
Parameter	*Ratio*	*Lower Limit*	*Upper Limit*
AUC 0-t	101.0	89.4	115.0
AUC 0-inf	102.0	90.4	116.0
Cmax	98.5	87.5	111.0

Protocol 95-166 - Single Dose Fasting - Desacetyldiltiazem (Metabolite I)

Linear Plot -



Semilog Plot -

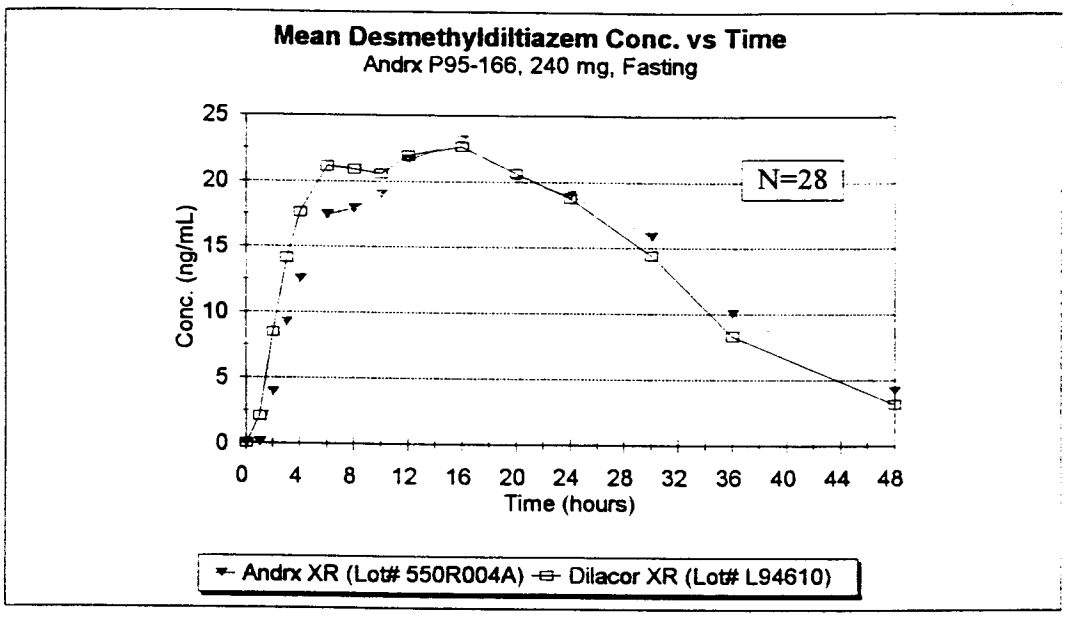


Summary of Test/Reference Ratios (as percents) and 90% Confidence Limits (N=28)

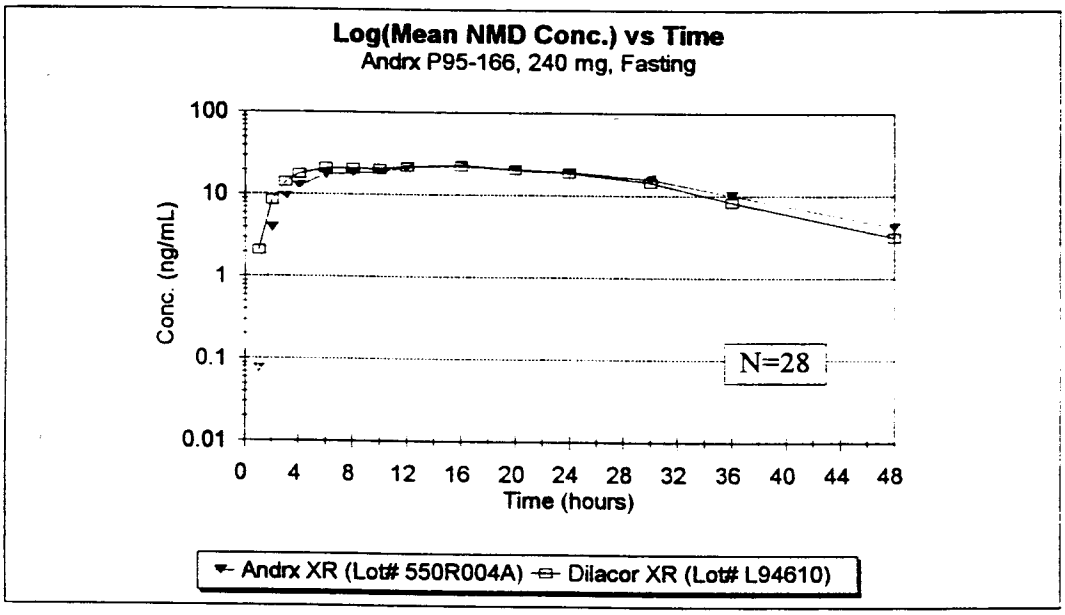
Parameter	*Ratio*	*Lower Limit*	*Upper Limit*
AUC 0~t	100.0	88.9	113.0
AUC 0~inf	107.0	97.3	118.0
Cmax	99.2	89.9	110.0

Protocol 95-166 - Single Dose Fasting - Desmethyldiltiazem (Metabolite II)

Linear Plot -



Semilog Plot -

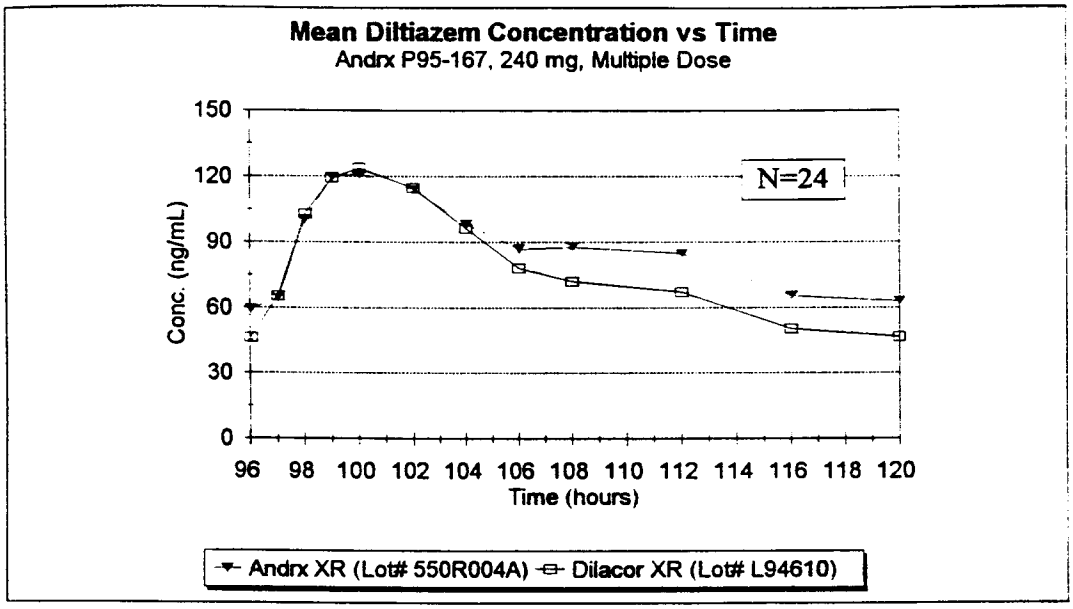


Summary of Test/Reference Ratios (as percents) and 90% Confidence Limits (N=28)

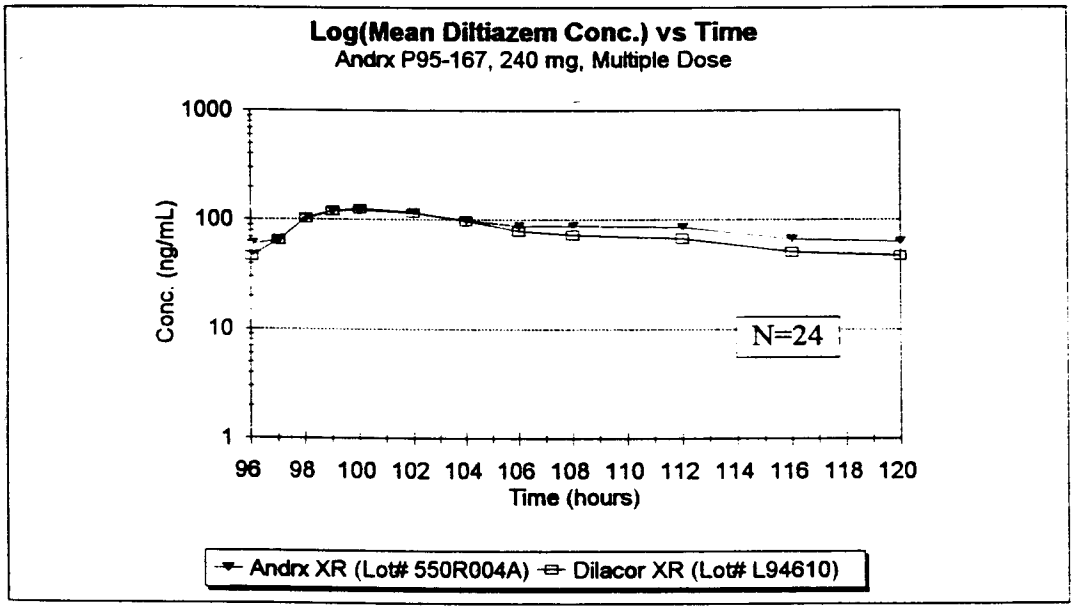
Parameter	*Ratio*	*Lower Limit*	*Upper Limit*
AUC 0~t	100.0	90.8	111.0
AUC 0~inf	102.0	93.0	112.0
Cmax	99.3	90.1	109.0

Protocol 95-167 - Multiple Dose Fasting - Diltiazem

Linear Plot -



Semilog Plot -

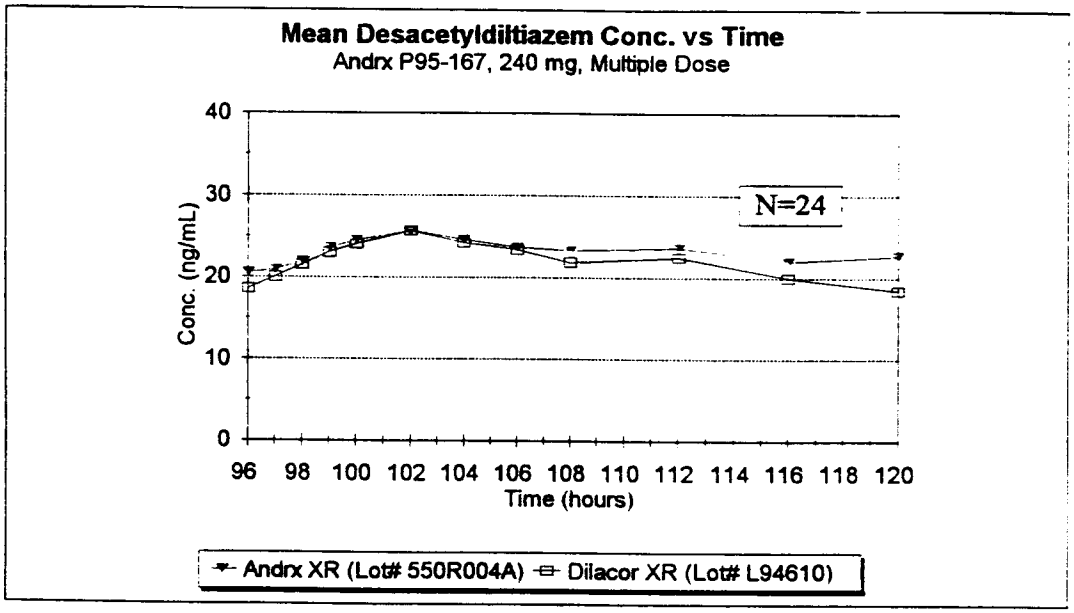


Summary of Test/Reference Ratios (as percents) and 90% Confidence Limits (N=24)

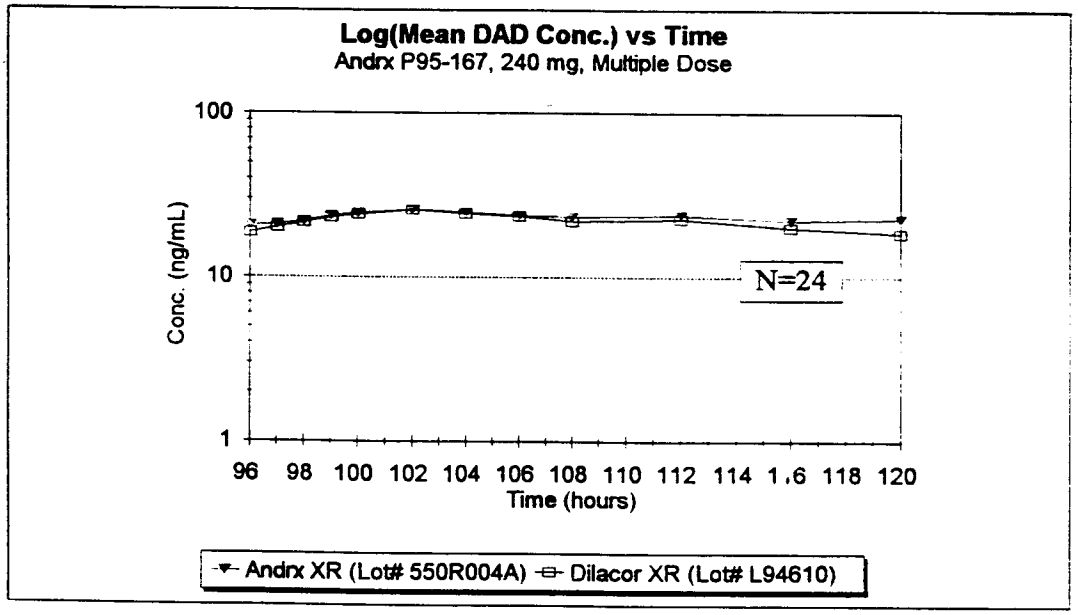
Parameter	*Ratio*	*Lower Limit*	*Upper Limit*
AUCinterdose	110.0	106.0	115.0
Cmax	101.0	94.2	109.0

Protocol 95-167 - Multiple Dose Fasting - Desacetyldiltiazem (Metabolite I)

Linear Plot -



Semilog Plot -

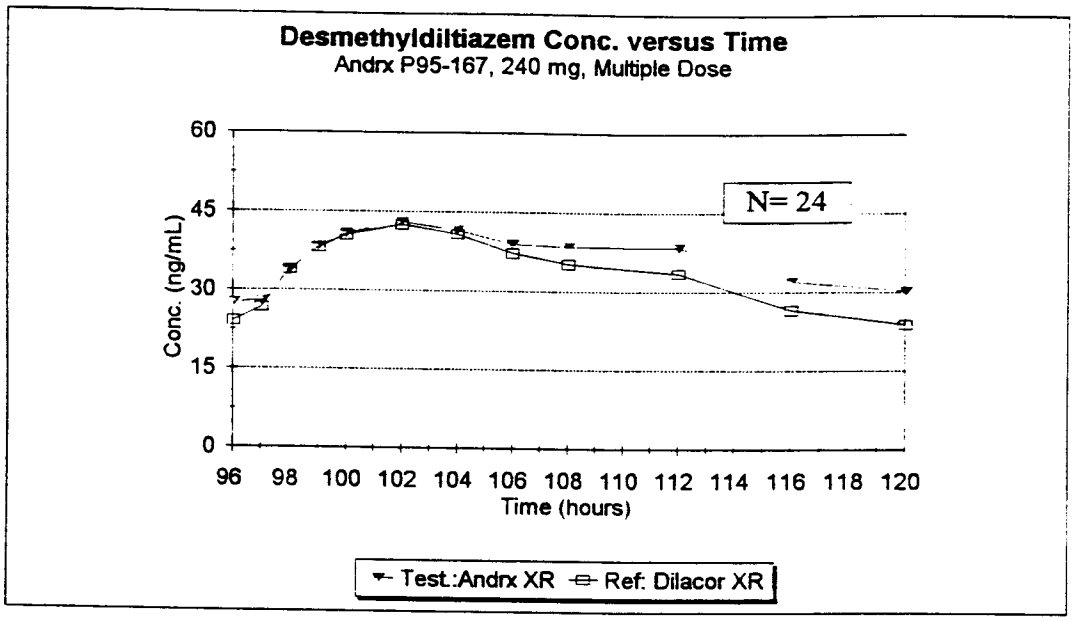


Summary of Test/Reference Ratios (as percents) and 90% Confidence Limits (N=24)

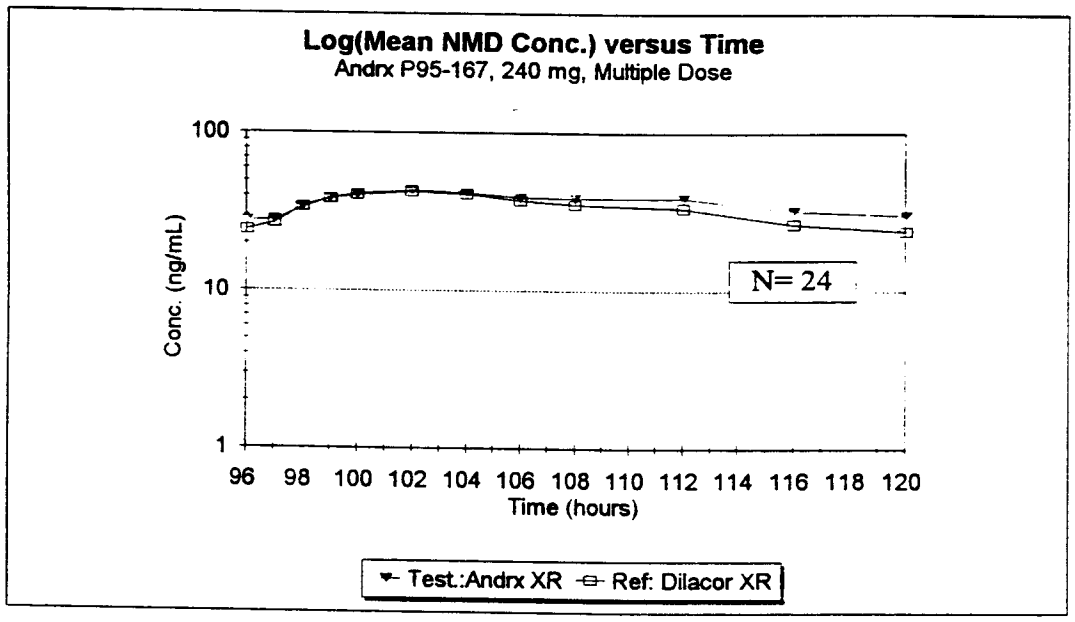
Parameter	*Ratio*	*Lower Limit*	*Upper Limit*
AUCinterdose	106.0	99.9	111.0
Cmax	101.0	94.2	107.0

Protocol 95-167 - Multiple Dose Fasting - Desmethyldiltiazem (Metabolite II)

Linear Plot -



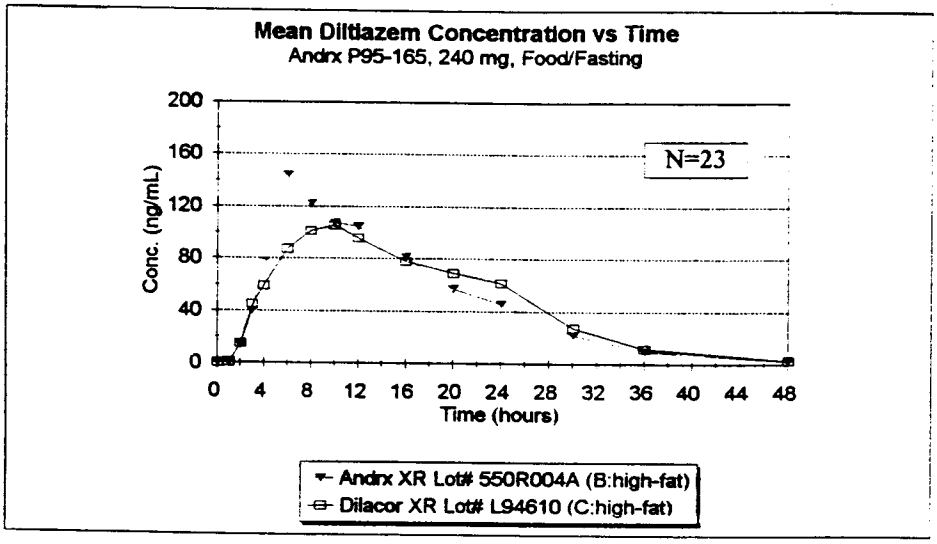
Semilog Plot -



Summary of Test/Reference Ratios (as percents) and 90% Confidence Limits (N=24)

Parameter	*Ratio*	*Lower Limit*	*Upper Limit*
AUCinterdose	108.0	104.0	112.0
Cmax	102.0	97.0	108.0

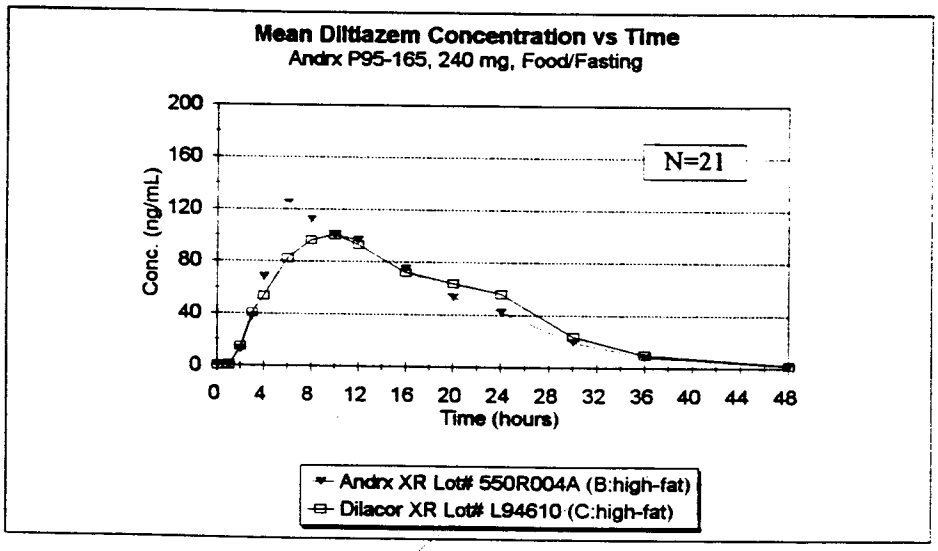
Linear Plot - All Subjects (Total = 23)



Summary of Statistical Analysis Results, N=23

Parameter	Test	Reference	% Difference
AUC 0-t	2,196.98	2,174.13	1.1
AUC 0-inf	2,237.33	2,217.57	0.9
Cmax	154.95	119.17	30.0

Linear Plot - Excluding Subjects 6 and 17 (Total = 21)

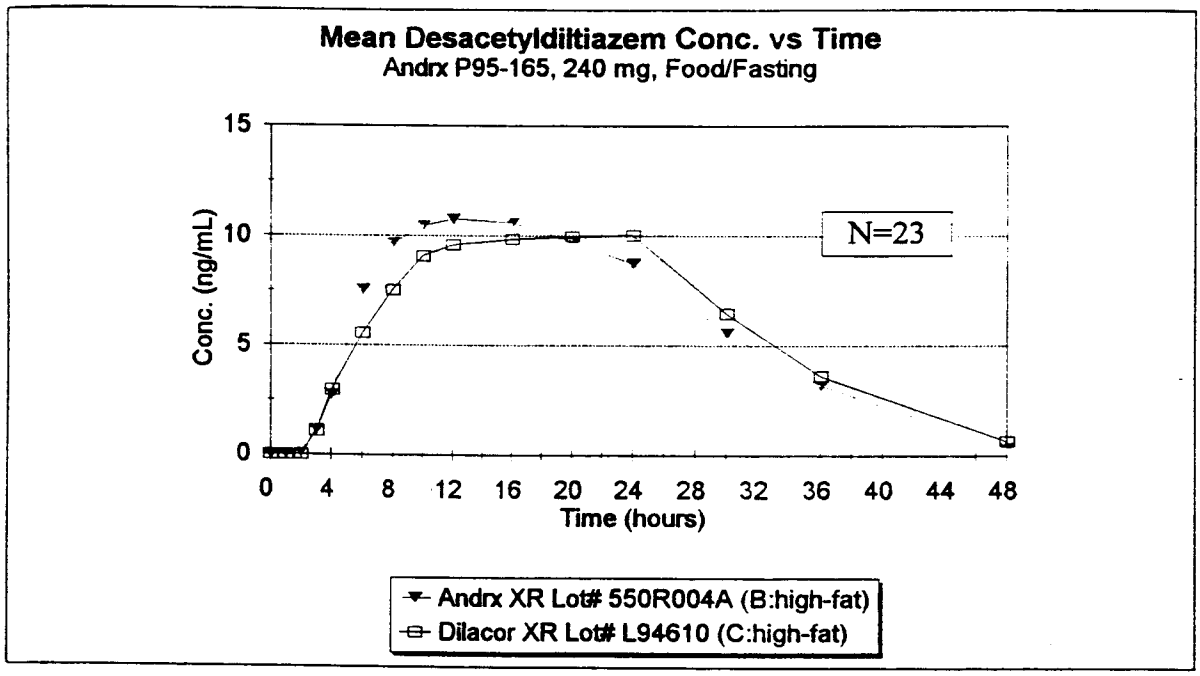


Summary of Statistical Analysis Results, N=21

Parameter	Test	Reference	% Difference
AUC 0-t	2,017.20	2,031.83	-0.7
AUC 0-inf	2,054.22	2,069.14	-0.7
Cmax	138.42	115.48	19.9

Protocol 95-165 - Single Dose Three-Way Crossover Food/Fasting - Desacetyldiltiazem (Metabolite I)

Linear Plot - All Subjects (Total = 23)

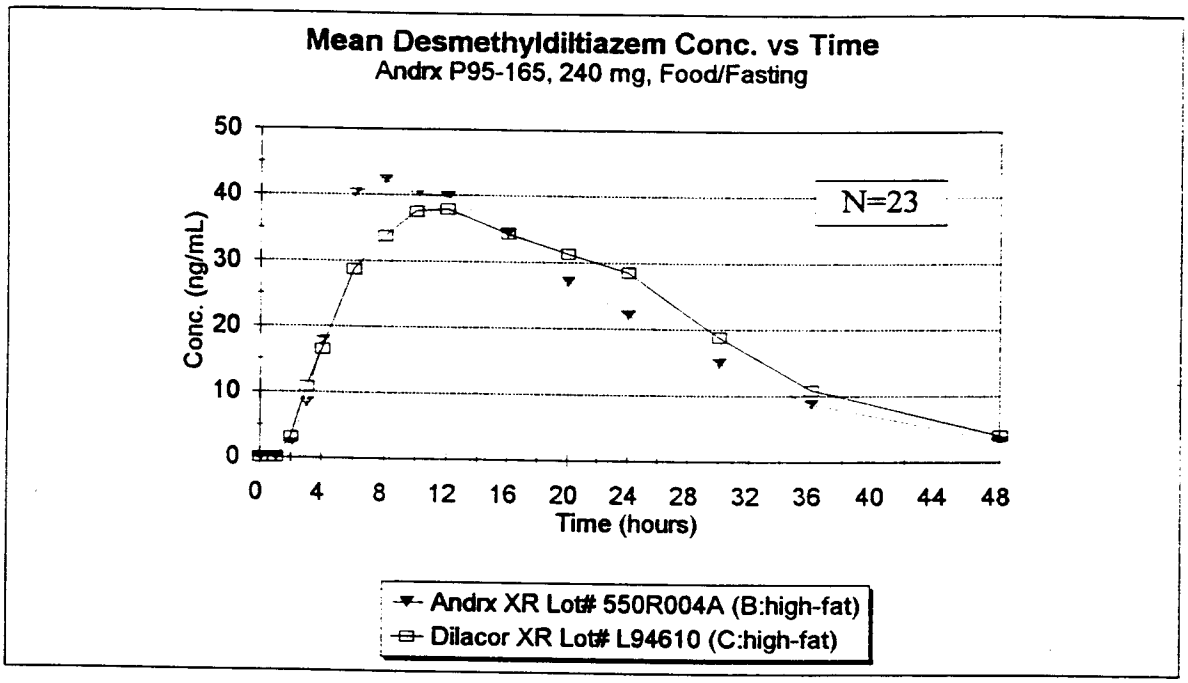


Summary of Statistical Analysis Results, N=23

Parameter	*Test*	*Reference*	*% Difference*
AUC 0~t	262.49	264.94	-0.9
AUC 0~inf	299.17	303.94	-1.6
Cmax	11.74	11.44	2.6

Protocol 95-165 - Single Dose Three-Way Crossover Food/Fasting - Desmethyldiltiazem (Metabolite II)

Linear Plot - All Subjects (Total = 23)



Summary of Statistical Analysis Results, N=23

Parameter	*Test*	*Reference*	*% Difference*
AUC 0~t	932.85	980.75	-4.9
AUC 0~inf	977.80	1,033.19	-5.4
Cmax	46.73	41.58	12.4

Table XII

000246

Dissolution Data of Diltiazem HCl Extended-release Capsules
Test and Reference Products

Method: USP 23, Apparatus 2 (paddles) @ 100 rpm, n=12 **Medium:** Water

Test Product: Andrx **Lot No.:** 550R004 **Strength:** 240 mg

Amount Dissolved (%)

Time (H)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Min	Max	Mean	%RSD
0	#4 - Confidential business														0	
1															3	32.6
2															10	8.2
3															13	9.6
4															17	9.6
7															28	10.7
10															37	9.9
13															46	8.6
15															52	7.7
18															62	6.4
21															71	5.2
24															80	4.0

Reference Product: RPR **Lot No.:** L94610

Amount Dissolved (%)

Time(H)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Min	Max	Mean	%RSD
0	#4 - Confidential business														0	
1															13	5.4
2															23	4.2
3															31	3.5
4															39	3.3
7															62	2.9
10															80	2.9
13															92	2.7
15															96	2.6
18															99	2.6

Formulation Data

Dissolution Data of Diltiazem HCl Extended-release Capsules
Test and Reference Products

Method: USP 23, Apparatus 2 (paddles) @ 100 rpm, n=12

Test Product: Andrx **Lot No.:** 550R004 **Medium:** SGF **Strength:** 240 mg

Amount Dissolved (%)

Time (H)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Min	Max	Mean	%RSD
0															0	
1															1	50.9
2															5	46.0
3															10	36.0
4															17	28.9
7															42	14.8
10															65	8.4
13															83	5.2
15															91	3.7
18															99	1.9

#4 - Confidential business

Reference Product: RPR **Lot No.:** L94610

Amount Dissolved (%)

Time(H)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Min	Max	Mean	%RSD
0															0	
1															11	5.1
2															19	1.7
3															26	2.0
4															32	2.8
7															48	3.3
10															65	3.0
13															79	2.5
15															87	2.3
18															95	1.9

#4 - Confidential business

Dissolution Data of Diltiazem HCl Extended-release Capsules
Test and Reference Products

Method: USP 23, Apparatus 2 (paddles) @ 100 rpm, n=12

Medium: pH 4.2

Test Product: Andrx **Lot No.:** 550R004 **Strength:** 240 mg

Amount Dissolved (%)

Time (H)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Min	Max	Mean	%RSD
0	#4 - Confidential business														0	
1															2	49.2
2															7	24.2
3															15	15.2
4															24	11.4
7															51	5.3
10															73	2.9
13															89	1.8
15															96	1.2
18															100	1.1

Reference Product: RPR **Lot No.:** L94610

Amount Dissolved (%)

Time(H)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Min	Max	Mean	%RSD
0	#4 - Confidential business														0	101.7
1															12	5.7
2															22	3.1
3															30	2.6
4															38	2.8
7															58	2.8
10															75	3.1
13															87	3.1
15															93	2.9
18															98	2.5
21															101	2.2

DEC 6 1996

Diltiazem HCl XR Capsules
120 mg, 180 mg and 240 mg
ANDA #74-852
Reviewer: Moheb H. Makary
WP 74852SDW.996

Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL
Submission Date:
September 5, 1996

Review of An Amendment to Bioequivalence Study

I. Objective:

The firm has replied to the reviewer's comments made in the review of the December 19, 1995 submission (bioequivalence studes on Diltiazem HCl XR Capsules, 240mg, dissolution data and waiver requests).

II. Comment

The firm was advised to submit comparative dissolution profiles on its Diltiazem HCl XR Capsules, 120 mg, 180 mg and 240 mg generated in 900 ml of 0.1N HCl (USP method). The firm was asked to submit in detail the dissolution method or methods the firm plans to use along with the proposed dissolution specifications.

The firm submitted dissolution testing results using the above method. The dissolution testing results are summarized in Table I. Both the Andrx diltiazem capsules and Dilacor^{R} XR do not meet USP specifications.

The firm proposes a dissolution method using pH 4.2 buffer (acetate) and the dissolution specifications for routine release of its product Diltiazem HCl Extended-release Capsules. The proposed dissolution method and specification are shown below:

Dissolution Method

Apparatus:	USP 23 apparatus 2(paddle) at 100 rpm.
Medium:	pH 4.2 buffer(acetate)
Volume:	900 mL
Temperature:	37±0.5°C
Sampling Times:	1, 4, 10 and 15 hours

The dissolution testing results are shown in Table II.

Dissolution Specification

Time(hr)	Amount Dissolved
1	[redacted]#4 - [redacted]
4	
10	onfidenti

15 [redacted]#4 -[redacted]

The firm intends to submit this dissolution method to the USP as a new method for its product.

Reply to the Comment

Based on the submitted data, the following specifications are recommended:

Time(hr)	Amount Dissolved
1	[redacted]#4 -[redacted]
4	onfident
10	usines
15	

The firm's response to the comment is acceptable.

II. Recommendations:

1. The single-dose bioequivalence study #P95-166, conducted by Andrx Pharmaceuticals, Inc., on its Diltiazem HCl Extended-release (XR) 240 mg Capsules, lot #550R004A, comparing it to Dilacor XR^R 240 mg Capsules manufactured by Rhone-Poulenc Rorer has been found acceptable by the Division of Bioequivalence. The study demonstrates that Andrx's Diltiazem HCl XR Capsules, 240 mg is bioequivalent to Rhone-Poulenc Rorer's Dilacor XR^R 240 mg Capsules.

2. The multiple-dose steady-state bioequivalence study #P95-167, conducted by Andrx Pharmaceuticals, Inc., on its Diltiazem HCl Extended-release (XR) 240 mg Capsules, lot #550R004A, comparing it to Dilacor XR^R 240 mg Capsules manufactured by Rhone-Poulenc Rorer has been found acceptable by the Division of Bioequivalence. The study demonstrates that Andrx's Diltiazem HCl XR, Capsules 240 mg is bioequivalent to Rhone-Poulenc Rorer's Dilacor XR^R 240 mg Capsules.

3. The single-dose post-prandial bioequivalence study #P95-165, conducted by Andrx Pharmaceuticals, Inc., on its Diltiazem HCl Extended-release (XR) 240 mg Capsules, lot #550R004A, comparing it to Dilacor XR^R 240 mg Capsules manufactured by Rhone-Poulenc Rorer has been found acceptable by the Division of Bioequivalence. The study demonstrates that Andrx's Diltiazem HCl XR, Capsules 240 mg is bioequivalent to Rhone-Poulenc Rorer's Dilacor XR^R 240 mg Capsules.

4. The dissolution testing conducting by Andrx Pharmaceuticals, Inc., on its Diltiazem HCl Extended-release (XR), 240 mg, 180 mg and 120 mg Capsules, lot #550R004, 549R004 and 548R003, respectively, is acceptable. The formulations for the 180 mg and 120 mg strengths are proportionally similir to the 240 mg strength of the test product which underwent acceptable

bioequivalence testing. Waivers of the in vivo bioequivalence study requirements for the firm's Diltiazem HCl Extended-release (XR), 180 mg and 120 mg Capsules of the test products are granted. The Division of Bioequivalence deems Diltiazem HCl XR, Capsules 180 mg and 120 mg, manufactured by Andrx Pharmaceuticals, Inc., to be bioequivalent to Dilacor XR® Capsules 180 mg and 120 mg, respectively, manufactured by Rhone-Poulenc Rorer.

5. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of acetate buffer pH 4.2 at 37°C using USP 23 apparatus II (paddle) at 100 rpm. The test product should meet the following tentative specifications:

Time(hr)	Amount Dissolved
1	[redacted]
4	
10	
15	

The firm should be informed of the above recommendations.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE /S/
FT INITIALLED RMHATRE
Date: 12/2/96

/S/

Concur: _____ Date: 12/6/96
Rabindra Pathak, Ph.D.
Acting Director
Division of Bioequivalence

MMakary/12-2-96 wp 74852SDW.996
cc: ANDA #74-852, original, HFD-658 (Makary), Drug File, Division File.

Table I

Table 1A. Dissolution Test Results of Diltiazem 240 mg Capsules in 0.1 N HCl

Time (hr)	Amount Dissolved (%)						USP Test #3 Spec.
	Mean		Range		%CV		
	Andrx[a]	RPR[b]	Andrx	RPR	Andrx	RPR	
6	29	46	[redacted]#4 - [redacted]		13.5	5.3	[redacted]#4 -
12	77	78	Confidentia		3.8	4.4	nfiden
18	99	98	[redacted]business[redacted]		1.6	2.6	usines

[a] Lot# 550R004
[b] Dilacor XR, Lot# L94610

Table 1B. Dissolution Test Results of Diltiazem 180 mg Capsules in 0.1 N HCl

Time (hr)	Amount Dissolved (%)						USP Test #3 Spec.
	Mean		Range		%CV		
	Andrx[a]	RPR[b]	Andrx	RPR	Andrx	RPR	
6	30	49	[redacted]#4 - [redacted]		17.1	5.3	[redacted]#4 -
12	78	84	Confidentia		5.9	4.7	onfident
18	100	103	[redacted]business[redacted]		2.5	2.1	ousiness

[a] Lot# 549R004
[b] Dilacor XR, Lot# L99407

Table 1C. Dissolution Test Results of Diltiazem 120 mg Capsules in 0.1 N HCl

Time (hr)	Amount Dissolved (%)						USP Test #3 Spec.
	Mean		Range		%CV		
	Andrx[a]	RPR[b]	Andrx	RPR	Andrx	RPR	
6	41	49	[redacted]#4 - [redacted]		12.5	3.3	[redacted]#4 -
12	86	81	Confidential		4.1	3.4	nfiden
18	104	97	[redacted]business[redacted]		1.2	2.6	usines

[a] Lot# 548R003
[b] Dilacor XR, Lot# L85912

Table II

000248

Dissolution Data of Diltiazem HCl Extended-release Capsules
Test and Reference Products

Method: USP 23, Apparatus 2 (paddles) @ 100 rpm, n=12

Medium: pH 4.2

Test Product: Andrx **Lot No.:** 550R004 **Strength:** 240 mg

Amount Dissolved (%)

Time (H)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Min	Max	Mean	%RSD
0	#4 - Confidential business														0	
1															2	49.2
2															7	24.2
3															15	15.2
4															24	11.4
7															51	5.3
10															73	2.9
13															89	1.8
15															96	1.2
18															100	1.1

Reference Product: RPR **Lot No.:** L94610

Amount Dissolved (%)

Time(H)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Min	Max	Mean	%RSD
0	#4 - Confidential business														0	101.7
1															12	5.7
2															22	3.1
3															30	2.6
4															38	2.8
7															58	2.8
10															75	3.1
13															87	3.1
15															93	2.9
18															98	2.5
21															101	2.2

Table II

000255

Dissolution Data of Diltiazem HCl Extended-release Capsules
Test and Reference Products

Method: USP 23, Apparatus 2 (paddles) @ 100 rpm, n=12

Test Product: Andrx **Lot No.:** 549R004 **Medium:** pH 4.2 **Strength:** 180 mg

Amount Dissolved (%)

Time (H)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Min	Max	Mean	%RSD
0															0	
1															2	22.0
2															10	10.9
3															19	6.3
4															28	4.5
7															54	3.0
10															75	2.2
13															91	1.4
15															97	1.0
18															100	0.9

#4 - Confidential business

Reference Product: RPR **Lot No.:** L99407

Amount Dissolved (%)

Time(H)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Min	Max	Mean	%RSD
0															0	
1															13	6.2
2															23	3.3
3															31	2.6
4															39	2.4
7															60	2.7
10															78	3.0
13															90	3.0
15															96	2.7
18															101	2.3

#4 - Confidential business

Table II

Dissolution Data of Diltiazem HCl Extended-release Capsules
Test and Reference Products

Method: USP 23, Apparatus 2 (paddles) @ 100 rpm, n=12

Test Product: Andrx Lot No.: 548R003 Medium: pH 4.2 Strength: 120 mg

Amount Dissolved (%)

Time (H)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Mean	%RSD
0													0	
1													3	17.7
2													10	10.6
3													18	8.2
4													27	7.6
7													54	4.4
10													74	2.8
13													91	1.4
15													97	1.0
18													101	1.0

#4 - Confidential business

Reference Product: RPR Lot No.: L85912

Amount Dissolved (%)

Time(H)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Mean	%RSD
0													0	
1													16	2.2
2													26	2.9
3													34	3.8
4													42	4.0
7													62	4.1
10													78	3.5
13													90	2.9
15													95	2.4
18													100	1.7

#4 - Confidential business

Table I

Table 1A. Dissolution Test Results of Diltiazem 240 mg Capsules in 0.1 N HCl

Time (hr)	Amount Dissolved (%)						USP Test #3 Spec.
	Mean		Range		%CV		
	Andrx[a]	RPR[b]	Andrx	RPR	Andrx	RPR	
6	29	46	[redacted]#4 - [redacted]		13.5	5.3	[redacted]#4 - [redacted]
12	77	78	Confidentia		3.8	4.4	nfider
18	99	98	[redacted]business[redacted]		1.6	2.6	usines

[a] Lot# 550R004
[b] Dilacor XR, Lot# L94610

Table 1B. Dissolution Test Results of Diltiazem 180 mg Capsules in 0.1 N HCl

Time (hr)	Amount Dissolved (%)						USP Test #3 Spec.
	Mean		Range		%CV		
	Andrx[a]	RPR[b]	Andrx	RPR	Andrx	RPR	
6	30	49	[redacted]#4 - [redacted]		17.1	5.3	[redacted]#4 - [redacted]
12	78	84	Confidential		5.9	4.7	nfident
18	100	103	[redacted]business[redacted]		2.5	2.1	usines

[a] Lot# 549R004
[b] Dilacor XR, Lot# L99407

Table 1C. Dissolution Test Results of Diltiazem 120 mg Capsules in 0.1 N HCl

Time (hr)	Amount Dissolved (%)						USP Test #3 Spec.
	Mean		Range		%CV		
	Andrx[a]	RPR[b]	Andrx	RPR	Andrx	RPR	
6	41	49	[redacted]#4 - [redacted]		12.5	3.3	[redacted]#4 - [redacted]
12	86	81	Confidential		4.1	3.4	nfiden
18	104	97	[redacted]business[redacted]		1.2	2.6	usines

[a] Lot# 548R003
[b] Dilacor XR, Lot# L85912

Table II

000248

Dissolution Data of Diltiazem HCl Extended-release Capsules
Test and Reference Products

Method: USP 23, Apparatus 2 (paddles) @ 100 rpm, n=12 **Medium:** pH 4.2

Test Product: Andrx **Lot No.:** 550R004 **Strength:** 240 mg

Amount Dissolved (%)

Time (H)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Min	Max	Mean	%RSD
0	#4 - Confidential business														0	
1															2	49.2
2															7	24.2
3															15	15.2
4															24	11.4
7															51	5.3
10															73	2.9
13															89	1.8
15															96	1.2
18															100	1.1

Reference Product: RPR **Lot No.:** L94610

Amount Dissolved (%)

Time(H)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Min	Max	Mean	%RSD
0	#4 - Confidential business														0	101.7
1															12	5.7
2															22	3.1
3															30	2.6
4															38	2.8
7															58	2.8
10															75	3.1
13															87	3.1
15															93	2.9
18															98	2.5
21															101	2.2

Table II

000255

Dissolution Data of Diltiazem HCl Extended-release Capsules Test and Reference Products

Method: USP 23, Apparatus 2 (paddles) @ 100 rpm, n=12

Test Product: Andrx **Lot No.:** 549R004 **Medium:** pH 4.2 **Strength:** 180 mg

Amount Dissolved (%)

Time (H)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Min	Max	Mean	%RSD
0															0	
1															2	22.0
2															10	10.9
3															19	6.3
4															28	4.5
7															54	3.0
10															75	2.2
13															91	1.4
15															97	1.0
18															100	0.9

#4 - Confidential business

Reference Product: RPR **Lot No.:** L99407

Amount Dissolved (%)

Time(H)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Min	Max	Mean	%RSD
0															0	
1															13	6.2
2															23	3.3
3															31	2.6
4															39	2.4
7															60	2.7
10															78	3.0
13															90	3.0
15															96	2.7
18															101	2.3

#4 - Confidential business

Table II

000262

Dissolution Data of Diltiazem HCl Extended-release Capsules
Test and Reference Products

Method: USP 23. Apparatus 2 (paddles) @ 100 rpm, n=12

Test Product: Andrx **Lot No.:** 548R003 **Medium:** pH 4.2 **Strength:** 120 mg

Amount Dissolved (%)

Time (H)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Mean	%RSD
0													0	
1													3	17.7
2													10	10.6
3													18	8.2
4													27	7.6
7													54	4.4
10													74	2.8
13													91	1.4
15													97	1.0
18													101	1.0

#4 - Confidential business

Reference Product: RPR **Lot No.:** L85912

Amount Dissolved (%)

Time(H)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Min	Max	Mean	%RSD
0															0	
1															16	2.2
2															26	2.9
3															34	3.8
4															42	4.0
7															62	4.1
10															78	3.5
13															90	2.9
15															95	2.4
18															100	1.7

#4 - Confidential business

OCT - 6 1997

Diltiazem HCl XR Capsules
120 mg, 180 mg and 240 mg
ANDA #74-852
Reviewer: Moheb H. Makary
WP 74852SDW.D95

Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL
Submission Date:
December 19, 1995

MEETING's MINUTES

This is the summary of the discussions held at the meeting on October 1, 1997 regarding the clinical status of a subject in the post-prandial study and the higher food effect observed with the test formulation compared to that for the reference formulation. Attendees were: Mary Fanning, Rabindra Patnaik and Moheb Makary.

DISCUSSION

Some facts were discussed when the firm's single-dose bioequivalence study #P95-165 under fasting and nonfasting conditions was reviewed.

1. Among the subjects, Subject #6 exhibited a high Cmax value of 353 ng/mL versus a mean Cmax value of 156 ng/mL for diltiazem (DTM) upon treatment with the test product under nonfasting condition. The firm suggested this Cmax value of subject #6 was a result of an unusual decrease in metabolism of diltiazem to produce DAD and NMD by the liver for that treatment period. The subject revealed no clinical abnormalities except for a very slight elevation in SGPT value of 42 u/l. Excluding subject #6 from the statistical analysis of the study was not justified.

2. Subject #17 had a value of 101 u/l for SGPT at the end of the study. The firm claimed that the high value of SGPT is an indication of liver dysfunction which may be responsible for the unusually high Cmax value (343 ng/mL) for subject #17 upon treatment with the test product under nonfasting condition. In addition, upon follow-up on subject #17, it was discovered that subject #17 had consumed alcohol prior to collection of the exit sample which might have had potential effect on the study data.

Excluding subject #17 from the statistical analysis of the study is justified.

3. After excluding subject 17 from the statistical analysis of the study, the resulting ratio of the test geometric mean to the reference mean geometric for Cmax is 1.24. This ratio is within the acceptable range of 0.80-1.25 for diltiazem under nonfasting condition.

4. The results indicate that the incidences of adverse experiences by the subjects were similar between the test and reference products in the study. None of the adverse events was considered serious or resulted in dropping any subject from the study.

5. Systolic and diastolic blood pressure, heart rate and percent change from baseline of the ECG PR interval were measured prior to dosing and during the study. In assessing the subjects and reported values for heart rate and blood pressure, there were no clinically significant differences in the parameters evaluated.

/S/

Moheb H. Makary, Ph.D.
Review Branch III
Division of Bioequivalence

/S/ 10/6/97

Ramakant Mhatre, Ph.D
Team Leader Review Branch III
Division of Bioequivalence

/S/ 10/6/97

Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-852 SPONSOR: AndrX
DRUG: Diltiazem HCl XR
DOSAGE FORM: Capsules
STRENGTH(s): 120 mg, 180 mg and 240 mg
TYPE OF STUDY: Single/Multiple Fasting/Fed
STUDY SITE: [redacted] #4 - [redacted] Confidentia

STUDY SUMMARY: The three bioequivalence studies conducted on AndrX's Diltiazem HCl XR Capsule are acceptable. The studies demonstrate that AndrX's Diltiazem HCl XR Capsules 240 mg is bioequivalent to Rhone-Poulenc Rorer's Dilacor XR 240 mg Capsule.

DISSOLUTION: Dissolution testing is acceptable. Waivers for the 120 mg and 180 mg strengths are granted

PRIMARY REVIEWER: [redacted] /S/ BRANCH: III

INITIAL: [redacted] /S/ DATE: 9/19/97

BRANCH CHIEF: BRANCH:

INITIAL: [redacted] /S/ DATE: 9/19/97

fw DIRECTOR
DIVISION OF BI[redacted]

INITIAL: [redacted] /S/ DATE: 10/6/97

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: DATE:

MAY 16 1997

Diltiazem HCl XR Capsules
120 mg, 180 mg and 240 mg
ANDA #74-852
Reviewer: Moheb H. Makary
WP 74852SDW.996

Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL
Submission Date:
April 24, 1997

Review of An Amendment to Bioequivalence Study

The firm accepted the tentative dissolution specifications provided by the Division of Bioequivalence, at this time. However, the firm indicated that it reserves the right to discuss this matter in the future, especially when the 24 month room temperature data are available for the biobatch and the first three commercial batches.

Based on the dissolution data submitted by the firm in the original submission, the following tentative specifications were recommended by the Division of Bioequivalence:

Time(hr)	Amount Dissolved
1	[redacted]#4 - [redacted]
4	Confidentia
10	business
15	

In this amendment, the firm proposed the following dissolution specifications:

Time(hr)	Amount Dissolved
1	[redacted]#4 - [redacted]
4	Confidentia
10	business
15	

Since the firm has not submitted additional dissolution testing results to support the above proposed changes in the dissolution specifications, the tentative dissolution specifications by the Division of Bioequivalence are recommended. The Division of Bioequivalence will consider the dissolution specifications submitted by the firm at a later time when additional data are available.

Recommendation:

The Division of Bioequivalence agrees with the firm that any changes in the tentative dissolution specifications for Diltiazem HCl XR Capsules, 120 mg, 180 mg and 240 mg, should be based on additional dissolution data. Therefore, the Division of Bioequivalence is looking forward for additional dissolution

testing results.

The firm should be informed of the above recommendation.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/ Date: 5/12/97

/S/

Concur: Date: 5/16/97
Nicholas Fleischer, Ph.D.
Acting Director
Division of Bioequivalence

MMakary/5-9-97 wp 74852SDW.497
cc: ANDA #74-852, original, HFD-658 (Makary), Drug File, Division File.

ANDA 74-852

DEC 24 1996

Andrx Pharmaceuticals, Inc
Attention: David A. Gardner
4001 SW 47th Avenue, Suite 201
Fort Lauderdale, FL 33314

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Diltiazem Hydrochloride Extended release Capsules 120 mg, 180 mg and 240 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 ml of acetate buffer pH 4.2 at 37°C using USP 23 apparatus II (paddle) at 100 rpm. The test product should meet the following tentative specifications:

Time(hr)	Amount Dissolved
1	#4 - Confidential business
4	
10	
15	

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research